ANNUAL REVIEW OF MEDICINE

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PREFACE

Although there have been additional changes in editorial personnel, it is expected that the policies previously established for the *Annual Review of Medicine* will be continued. In brief, authors both in this country and abroad will be selected to review important segments of medicine regularly; they will be asked, as in the past, to write for physicians and surgeons who strive to keep abreast of progress in medicine's diverse fields.

The present editors wish to acknowledge a debt to their predecessors who have shown the way by establishing the *Review* in the good graces of so many readers, and hope that future chapters measure up to the best of those which now appear or which have gone before.

Finally, we are most grateful to Mrs. Mary Jean Van Peborgh and her associates in the Editor's Office.

W.C.C. R.M.
K.S G. S.C.M.
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The *Edinburgh Medical and Surgical Journal* first appeared on January 1, 1805. In the "Advertisement" with which this issue opens it is stated that the object of the editors is "the improvement of Medicine by collecting the scattered hints and registering the important facts connected with Medical Literature and Medical Practice " That the modern oft-repeated lament about the great number of scientific journals is nothing new becomes clear in a later part of the Advertisement which says "The custom of declaiming against the multitude of similar publications is unreasonable Their very existence is a proof that their utility is felt and acknowledged." The first number of the *Lancet* was issued on October 5, 1823 as a medium "which would convey to the Public and to distant Practitioners as well as to Students in Medicine and Surgery reports of the Metropolitan Hospital Lectures" (p 1) It was also to be a medium for "unpublished cases, whether in England or any part of the civilized Continent" (p 1). The opening article from the Theatre at St Thomas Hospital begins on a truly dramatic note: "At half past Seven this Theatre was crowded in every part by upward of four hundred Students of the most respectable description, in fact we never before witnessed so genteel a Surgical class . . About Eight o'clock Sir Astley Cooper arrived . . " (to give his lecture) The early numbers of the *Lancet* dealt, however, not only with medical matters but with literary and musical criticism, chess problems, and there were also columns of comments on various miscellaneous matters The *Glasgow Medical Journal* opened its pages in February 1828 and the *Guy's Hospital Reports* began in 1836 with an introductory article by Dr Barlow, one of the editors, entitled "On the advantage of recorded experience in Medical Science "

On this side of the water Carey, Lea, and Carey of Chestnut Street, Philadelphia launched the *American Journal of Medical Sciences* in 1827. There are at times criticisms of current Journals because they "beat the bushes" for material and even pay for articles; it is interesting to discover that this procedure is by no means new since in the advertisement preceding the first number of the *American Journal* it is stated "In respectfully inviting contributions from every part of the Union the publishers . now repeat the assurance that all articles that may be inserted will be liberally

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paid for." On the whole, however, the early journals seem to have been media for voluntary contributions. The *Boston Medical and Surgical Journal* appeared in the following year—February 19, 1828, and began quite abruptly without introduction or advertisement with an article on "Cases of Neuralgia or Painful Affections of the Nerves" by John C. Warren At the top of the page is the engraving of the old Massachusetts General Hospital which still heads the Case Reports section in the *New England Journal of Medicine.*

In France on January 2, 1830 in a time of political turmoil appeared the first number of the *Gazette Médicale de Paris* which opened with a florid semi-political introduction by Jules-Guérin. On this same front page, under the heading "Feuilleton," is an article entitled "Histoire d'une poule à profile humain."

The Germans early realized that the mass of material in medical journals was getting out of hand and by 1843 there already was started a "review journal"—*Jahresbericht uber die Fortschritte der gesamten Medicin in allen Ländern.* This was the precursor of the famous German abstract journals—the *Zentralblatter*—of the turn of the century. The *Berliner klinische Wochenschrift* in an introductory page entitled "Programm" justified its inception (1864) by the statment that a division of labor was now necessary. The editor, Posner, asked for "original clinical communications" "aus allen Gebieten der innere und auseren Heilkunde." Other special journals were soon founded, such as the *Deutsches Archiv für klinische Medicin* (1866), the *Jahrbuch für klinische Medicin* (1866), the *Jahrbuch für Kinderheilkunde und physische Erziehung* (1868), the first article in which was "On the study of children's disease and on children's hospitals " The *Deutsche Zeitschrift für Chirurgie* was first published in 1872

Review and abstract journals became necessary in the preclinical sciences also and in 1873 there was founded the *Jahresberichte über die Fortschritte der Anatomie und Physiologie,* and in 1877 *Hoppe-Seyler's Zeitschrift für physiologische Chemie* saw the light The *Deutsche medicinische Wochenschrift,* however, was not founded until 25 September 1875. Meanwhile special journals were appearing in England such as the *Journal of Anatomy and Physiology* (1868).

Our own *Journal of the A.M A.* did not start until July 14, 1883. It is of interest that the *Transactions of the Iowa State Medical Society* appeared as early as 1871 (Davenport, Iowa) as a neat volume which opened with an address by J W H. Baker entitled "Medicine not an exact science."

One can see, then, from this sketchy summary, the pattern along which medical journals developed first as media for the publication of any phase of the subject, to be followed by special magazines and finally by publications of reviews or abstracts During the first part of this century there was what one might call a normal increase in the number of journals but since World War II there has been a multiplication of almost unbelievable volume. Almost every disease, nay, almost every phase of each disease has its own journals; a similar proliferation is obvious in the pre-clinical and funda-

mental sciences. New journals seem to appear every month. Today the Lane Library, whose stacks are by no means complete, subscribes to some 2000 journals.

The reasons for this frantic increase are not far to seek. First of all the fruits of a vast increase in research activity require a medium for publicity. During the war the needs of national security demanded extensive studies of new drugs, prophylactic measures against infections and technical methods of all sorts. The machinery of implementing such a program was set up; new laboratories were built, a new system of fellowships was devised and funds, first from Government and later from private sources, were furnished in increasing amounts in an era of great financial prosperity. This machinery has not only been kept in operation but it is increasing from day to day. Not only are Government funds constantly appropriated with more liberality, but the public fancy has been caught so that lay organizations of every sort are able to collect funds for support of research. The American Heart Association, to mention one example, has been most successful in collecting and in distributing large sums of research money.

Still other influences are at work in increasing the output of publications. One of the most potent of these is the large pharmaceutical houses. New groups of drugs are put out in great profusion. Not only the merits but the safety of these agents must be appraised and as soon as the popularity of one group wanes it is sure to be replaced, like the Hydra, by others. Huge numbers of papers describing the merits of such medicaments, now obsolete, are buried in recent journals

Another form of modern medical journal is that which is essentially a commercial venture. While such journals often carry excellent and useful articles these are not as a rule spontaneous contributions but are solicited by the editorial staffs and are often paid for Some of these journals have borrowed the methods of the popular lay weeklies and have introduced the "cartoon" method of emphasizing their points

The result of this vast plethora of medical writing, now completely out out of hand from the standpoint of the potential reader, is a frantic attempt on all sides to concentrate, abbreviate, abstract, and condense a subject in such fashion that the doctor has some faint chance of covering the ground Some of these attempts are good and useful; others unfortunately introduce a new form of distemper: The reviewer or compiler faced by a vast and often highly specialized literature issues an article which is little more than a list of titles, and which is really almost useless

It is at this point that the *Annual Review of Medicine* has its unique *opportunity* Let us make a few comments about the ideal review. First of all there is to be considered what sort of research is worth while, what publications are worthy of recognition. It seems to us that there are three specifications requisite for true research First, the investigator must have a question for answer Too often he only has a method which he applies more or less at random. True his observations have never been made before

but the mere fact of novelty does not guarantee value. The literature is cluttered with material of this sort, much of which is meaningless Second, the question asked must be of a sort which can be answered by available methods. "What is life?" for example, would be a perfectly good question but unfortunately we have not the methods to answer it. Third, the question when answered must give *information* which general opinion regards as worthwhile. Many so-called "projects" for example yield results which seem of little value. We scratch our heads and are forced to agree with Dean Swift whose savage satire over 200 years ago conferred an immortality of ridicule on the project system.

It is obvious then that the reviewer must carefully select the useful and important contributions; he must weave them into something of a coherent whole. He must assume that his readers are not already familiar with the intimate details of the subject; the universe of discourse must be defined for them. It is his task to synthesize the important advances in a subject in such fashion that a vivid story captures the reader's interest. As we said above no mere catalogue of titles will suffice.

In the past most of the writers in the *Annual Review of Medicine* have followed the general policy outlined above and many outstandingly helpful articles have appeared—not mere compilations but valuable syntheses of a subject We are sure that those selected to do reviews in the future will continue along the same lines

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INFECTIOUS DISEASES (VIRUSES)[1]

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Despite the increasing importance of this group of agents in the spectrum of human disease and the immense amount of research that is being conducted, significant contributions to the clinical understanding and management of these diseases accumulate slowly. The second edition of *Viral and Rickettsial Infections of Man* (1) has brought together for the clinician the available information on all these diseases up to 1952, supplementing the 1951 review by Burnet in the *Annual Review of Medicine* (2). The objective of this review has been to discuss in some detail certain significant new information that has become available since that time in regard to a few of these conditions. It is hoped that in this way the repetition of already known facts will be minimized. Where the 1954 review [Jawetz (3)] refers briefly to new facts about a disease these will be amplified in some cases. Discussion will be organized under the heading of the agent or group of related agents under consideration. Emphasis will be given to those facts which aid the clinician in the understanding and management of these diseases, and reference to technical advances will be largely limited to those which seem to bear directly on these points.

POLIOMYELITIS

Pathogenesis

Effect of immunization procedures on the incidence of poliomyelitis.—Burnet's review in 1951 (2) reported the Australian and British observations on the precipitation of paralytic poliomyelitis by immunizing injections. Since that time further studies have been carried out in the United States and Canada as well as in Australia and the United Kingdom. In the United States, Greenberg *et al.* (4) analyzed the inoculation histories of 1300 children that had had poliomyelitis in New York City 1949–1950. A relationship was shown to exist between the site of injection and the site of paralysis in children injected not more than a month before onset of poliomyelitis with diphtheria toxoid, pertussis vaccine, or tetanus toxoid, or any combination of the three. No such a relationship was clearly shown with the injection of penicillin or other agents. There was no increase of bulbar cases or deaths associated with the injections. Among 619 children with poliomyelitis, 56 (9 per cent) had been inoculated within one month whereas among a matched group without poliomyelitis only 21 (3.4 per cent) had been inoculated within one month. They considered that the risk of increasing poliomyelitis in children under one year was small (less than 3 per cent occurred under this age),

[1] The survey of literature for this Review was completed in July, 1954.

and under 6 months was negligible. Korns *et al.* (5), in a similar study of patients with poliomyelitis in New York State, excluding New York City, in the same year found that twice as many poliomyelitis cases had had injections during the two-months period before onset than had the controls without poliomyelitis, and that there was a positive correlation between the site of paralysis and site of injections. Although all injections were included, 60 per cent of them were for immunization against diphtheria, pertussis, and tetanus These authors emphasized that the increased risk is very slight. It would mean that out of 10,000 persons 9996 would escape poliomyelitis if they had been inoculated, whereas 9998 would escape if they had not received injections. Rhodes (6) summarized the cases of paralytic and non-paralytic poliomyelitis in Canada in 1951. He obtained immunization histories for 339 of 355 children seen in the Toronto Children's Hospital for poliomyelitis and found no correlation between paralysis and immunization. Rosen & Thooris (7) reported a higher incidence of leg paralysis during an epidemic in French Oceania in regions where intramuscular injections for Treponematosis were being given into the buttocks The importance of defining this relationship is clear because of the effect it might have on public health practices of preventive medicine and even therapeutic injections. The opinion of the United States Public Health Service (8) as promulgated in March 1952 can be summarized as follows. There was no evidence that there was any association between the injection of drugs or vaccines and paralytic poliomyelitis. There was evidence that inoculations for immunization against diphtheria, pertussis, and possibly tetanus might cause localization of paralysis in the inoculated arm or leg. Most of the associated inoculations had been given during a period of 7 to 21 days before the onset of paralysis, i.e , during the incubation period of the disease It was recommended that routine immunizations should not be withheld from infants under six months, or from others except in the face of an epidemic in the community. Naturally, attempts have been made to reproduce this effect in animals Melnick & Ledinko (9) found no association between vaccination and paralytic poliomyelitis in mice, monkeys, or chimpanzees, although it is pointed out that this failure did not deny its existence in human beings On the contrary, Bodian (10) injected 4 ml. of cortisone or a 1 5 per cent gelatin solution into the calf muscles of cynomolgus monkeys, and then infected them with Type I Mahoney strain by intracardiac inoculation He found an increased incidence of paralysis (1 6:1) and a localization of the paralysis in the injected limbs He suggested that the amount of material injected injured the muscle and allowed the virus to enter peripheral nerves from the blood stream.

Effect of tonsillectomy—Further studies have also been done on the association of tonsillectomy and the incidence of poliomyelitis It has been recognized for many years that recent tonsillectomy increases the risk of bulbar poliomyelitis (1). This has been further confirmed by Wilson (11) and Miller (12) and has been attributed to the trauma of the operation which exposed fibers of the glossopharyngeal nerve. However, reports of Top (13), South-

cott (14), Anderson & Rondeau (15) and Weinstein *et al.* (16) on new data, with a re-evaluation of older reports, emphasize that this relationship is not confined to recent tonsillectomy. Top reviewed 10 years experience in Detroit and reported an incidence of bulbar poliomyelitis of 20 4 per cent in 811 patients who had been tonsillectomized in the past, as opposed to 3.8 per cent in 936 patients who had not. The experiences of the other reporters were comparable. The last two groups of authors (15, 16) analyzed the incidence of bulbar poliomyelitis at different ages according to the presence or absence of tonsils They found that absence of tonsils was the only factor that could be correlated with bulbar poliomyelitis, the chance of getting bulbar poliomyelitis being 1:12 in the presence of tonsils and 1:3 in their absence, regardless of age. The apparent increase of this type of infection in older age groups merely reflects the increasing number of people who have been tonsillectomized with increasing age. The mechanism by which a long past tonsillectomy increased the localization of the virus in the bulbar region is quite obscure. Southcott (14) suggests that tonsillectomy disturbs the normal relationship of pharyngeal muscles and leaves muscle bundles in a more superficial position than normal, thus making them more easily accessible to the virus which appears to travel along the motor nerve fibers of the vagus to the nucleus ambiguus Histological evidence indicates that this motor nucleus is always more involved than the sensory nucleus dorsalis.

Neural invasion.—Faber *et al.* (17, 18) have done a number of experiments which they interpret as indicating that the neural infection is primary, and that viremia appears secondarily to centrifugal spread of the virus from the nervous system to the peripheral nerves. Certainly a primary neural infection would seem to be the most likely explanation of the association of tonsillectomy with bulbar poliomyelitis as was suggested by Southcott (14). It is possible that, whereas usually the central nervous system is infected from a viremia (see below), the direct neural route of invasion may also occur under certain circumstances. Because of the possibility that poliomyelitis virus might be introduced from the skin into peripheral nerve endings, Faber & Dong (19) investigated various antiseptics for their virucidal properties. They found 2 per cent tincture of iodine the most potent poliocidal substance, and recommend its routine use for preparation of the skin before an injection.

Viremia —Within the recent past evidence has accumulated that, contrary to the opinion of Faber *et al*, just reviewed, viremia occurs before the invasion of the central nervous system The detection of poliomyelitis virus in the blood of experimental animals which had been given virus orally had already been reported in 1952 (1) Bodian & Paffenbarger (20) and Horstmann *et al* (21) have reported the isolation of virus from the blood of human beings who were contacts of a case. The latter describe the isolation of Type I virus from the blood of 6 of 33 children, all known to be infected by the presence of Type I virus in rectal or throat swabs Of those with detectable viremia, four had symptoms of a minor illness which did not proceed to involvement of the cerebral nervous system, one had a minor illness that pro-

ceeded to central nervous system involvement without paralysis, and one was asymptomatic. Neutralizing antibody was found sometimes as early as the third day after onset of the symptoms of the "minor illness" These findings emphasize the varied clinical pictures associated with viremia, and suggest strongly but do not prove that extra-neural multiplication occurs before involvement of the central nervous system. These observations parallel those made in monkeys and chimpanzees, namely, that the virus appears very early in the blood after oral infections, sometimes as long as a week before paralysis [Bodian (22) and Horstmann (23)].

The importance of the concept of hematogenous spread of the virus is clearly far-reaching. Bodian (22) and Pette (24) reviewed the whole problem of pathogenesis as altered by this observation. They divided the disease into three stages (a) visceral, in which the virus multiplied in the mucous membranes of the oropharynx and ileum, (b) vascular, in which the virus invaded the blood stream or regional lymph nodes, and (c) neural, rare, in which the virus invaded the central nervous system

Prophylaxis

Gamma globulin —Bodian (25 to 28) showed that gamma globulin given in doses of as little as 0 1 ml per kg to monkeys and chimpanzees prevented viremia following oral administration of virus Hammon *et al* (29) reported protection in suckling mice from as little as 0 05 ml. per lb of body weight. Wood *et al* (30) showed that intramuscular injections of gamma globulin in doses of 0.1 to 0 4 ml per lb. of body weight into humans led to detectable antibody in their blood stream Hammon and his co-workers (31, 32, 33) carried out a large field study in which 55,000 children were inoculated Half were given gamma globulin in doses of 0 14 ml per lb on the average, and half were given equal amounts of a gelatin solution made up to resemble the gamma globulin exactly The study was set up in such a way as to insure complete randomization of the injected children without knowledge on the part of those doing the inoculation as to which vial was which When the results were analyzed, it appeared that 104 cases of clinically diagnosed paralytic poliomyelitis occurred among the injected children during a 14-week follow up. Of these, 31 occurred among the gamma globulin, and 73 among the control gelatin group, a significant difference During the period of the second to fifth weeks inclusive there were only seven cases in the gamma globulin group as opposed to 39 cases among the gelatin controls A later study [Hammon *et al* (34)], based on cases confirmed in the laboratory, revealed a rather greater protection from gamma globulin during this period, four in the gamma globulin group as opposed to 34 in the gelatin group Furthermore, although from the data provided by clinical diagnosis alone there was little evidence of protection beyond the end of the fifth week, significant protection extended to the end of the eighth week among the laboratory-diagnosed cases. Certain criticisms [Sabin (35)] were levelled at the conclusions drawn from this study chiefly on the basis that the acknowledged difference could have been due to an increase in cases induced by the inoculation of gelatin

This criticism seemed supported by the report of Bodian's experiments (10) (see earlier) in which he demonstrated that injection of gelatin led both to an increased incidence of paralysis and to localization of paralysis at the site of gelatin injection in monkeys. However, it should be emphasized that all the children received their inoculation in the right buttock, and no localization of paralysis was found among the children in either the gamma globulin or the gelatin inoculated groups Furthermore, the dose used by Bodian was such as to cause marked trauma of the muscles of the monkeys, a situation which did not apply in the children Also there was a seven-fold increase in the gelatin group over the gamma globulin group, whereas the difference in the monkeys was only 1 6 to 1. From the final analysis of the data one of the most important conclusions that can be drawn is that children inoculated with gamma globulin more than seven days and less than seven weeks before exposure (taken as the occurrence of a case in the family) did develop a non-paralytic infection as diagnosed by excretion of virus in the stool, by a rise in neutralizing- or complement-fixing antibody titer, or both, although they were protected from paralysis. The only difference between the gamma globulin injected children and the gelatin-control groups was that the gamma globulin group appeared to develop antibody rather more slowly than those not so inoculated, but eventually developed an equally high titer [Wehrle *et al* (36)] This paralleled the observations of Bodian (27) who reported that chimpanzees passively immunized with gamma globulin showed no decrease in the amount of virus excreted in the feces as compared with the controls, but developed no viremia. They also developed antibodies, but more slowly than the controls. The latter developed a high antibody titer within two weeks and thereafter decreased to a permanent level by two months. The protected animals lost their passive antibody during the course of the first two weeks, and then developed an active antibody reaching the level of that in the controls at two months

Following this demonstration, gamma globulin was used in 1953 in an attempt to influence outbreaks of disease in the United States, Hawaii, and Mexico Analysis of the figures in the United States (37) was not conclusive although the findings of the controlled study were not contradicted However, Hammon (38) reports results from Hawaii and Calderón *et al.* (38a) from Mexico that provide further evidence of its effectiveness in the field. Used in family contacts in the U S A , no protection was noted (37). Passive protection provided by gamma globulin is only temporary if the individual is not continually exposed to the virus, and as a public health measure would be extremely expensive It was estimated that, because of the relatively low incidence of paralytic poliomyelitis, even in an unusually severe epidemic approaching 1 per 100 children under 14 years of age [Bell (39)] such as occurred in Woodbury County, Iowa, and Dakota County, Nebraska, it would require 300 injections of gamma globulin to prevent one case of paralysis It was, therefore, logical that methods of providing active immunity should be explored

Vaccines.—Two main lines of work have been undertaken The first was

the development of a killed vaccine. Salk *et al.* (40) have succeeded in developing a formalin-inactivated vaccine, consisting of the three established types of poliomyelitis virus grown on monkey kidney tissue, which leads to a good antibody response in human beings. At the time of writing, reports are available on only a few children given vaccine seven months earlier. In these the antibody levels were well-maintained A booster effect was observed when vaccine was given to a subject who already had antibody from a previous natural infection [Salk (41)]. Milzer and co-workers (42) have reported obtaining a rise in antibodies in the majority of 30 adults from a vaccine combining all three types inactivated by ultraviolet light. The Salk vaccine is being used on an experimental scale on approximately 650,000 children between the ages of six to nine years, one-third being given placebos (43) The second approach is the development of modified or attenuated strains of virus which then can be given orally as live vaccines. Many experimental technics are being employed. One approach has been to use rodent-adapted strains. Type II has long been rodent-adapted and recently adaptation of both Type I [Li & Schaeffer (44); Koprowski *et al.* (45)] and Type III [Li & Habel (46); Li & Schaeffer (44); Casals *et al.* (47)] viruses to rodents has been accomplished by using spinal cord inoculation of mice with material that had been passed many times in monkey cell tissue culture. Such adapted viruses lost their pathogenicity for monkeys. Koprowski *et al.* (48, 49) have used a modified Type II virus, the "TN" strain, for oral immunization of 81 children They were successful in causing the development of specific antibodies in 70 without evidence of viremia or illness in any of them. Fourteen of these children were studied at intervals of up to three years later [Koprowski *et al.* (50)] and all showed a persistence of antibodies Koprowski *et al* (51) have also fed mouse-adapted Type I to three individuals without producing illness or viremia, but succeeded in establishing the virus in the stool and provoking antibodies On one patient the stool virus was found to be no more pathogenic for monkeys than the original strain Cox (52) has urged the advisability of a nonmammalian host for propagation of a vaccine. He reports the successful adaptation of a Type II strain to eggs by Roca-Garcia *et al* (53), Cabasso *et al.* (54), and Moyer *et al* (55). Sabin (56) has found that strains of all three types can be produced in tissue culture, by rapid passage of large inocula which are avirulent for monkeys, although large doses of such strains give rise to antibodies when fed to cynomolgus monkeys

Isolation and Identification

The tissue culture technics [see reviews by Sanders *et al* (57) and Rob- [illegible]

"Orphan" viruses.—The use of these technics for the isolation and identification of viruses from patients clinically diagnosed as suffering from poliomyelitis has revealed a number of unidentified viruses which are cytopathogenic for tissue cultures but not pathogenic for monkeys or rodents, and are not typed by the three standard sera. These "orphan" viruses have been found in the stools of patients by several workers [Melnick *et al* (62); Steigman, Kokko & Silverberg (63)] Of greater importance is the report of the isolation of such an agent from the brain and spinal cord of an infant dying of histologically characteristic poliomyelitis [Steigman *et al.* (64, 65)]. This latter finding raises the question concerning the possibility of other types of poliomyelitis virus which may affect man but were not identifiable when monkeys were the host used for typing.

Epidemiology

Numerous studies on the epidemiology of poliomyelitis have appeared during this period which have reemphasized previous reports that the age group of peak incidence tends to be higher in highly civilized communities in which the disease is epidemic, whereas in less civilized groups the disease appears to be endemic and peak incidence of infection occurs largely in infancy. These points have been well reviewed by Paul (66)

Family incidence.—Because of the findings that prophylaxis against paralytic poliomyelitis can be obtained by the use of gamma globulin, considerable thought was given as to the most efficient method of employing the limited stock at hand. One of the concepts was to give gamma globulin to family contacts This led to an analysis of the risk of the spread of infections in families. It appears that the spread of infection in a household is an explosive one, presumably the whole family being exposed to a subclinical case. As a result 80 per cent of secondary cases occur within seven days after the di-
[illegible]

from year to year, but averaged about 2.5 to 5 per cent. The risk of paralytic poliomyelitis in a family following the occurrence of the original case was calculated to be forty times as great as in the population at large [Siegel & Greenberg (67)]

Infection under six months—It has generally been considered that paralytic poliomyelitis under six months of age is very uncommon, but few figures were available. Two reports [Geffen & Tracy (68); Roberts & Thomson (69)] on the 1950 epidemic in England indicate that there were 82 such cases, 77 of them paralytic This is 56.6 per cent of the number which would have been expected if poliomyelitis were evenly distributed, by six-month periods, in the age groups from birth to 15 years. Although the incidence is about half the expected, the fatality rate in these infants was 23 per cent, or more than twice the fatality rate among older children Of the 58 survivors, 30 had severe or very severe paralysis and only two recovered completely. McConnell (70) records poliomyelitis in ten infants under six months out of a

the development of a killed vaccine. Salk *et al.* (40) have succeeded in developing a formalin-inactivated vaccine, consisting of the three established types of poliomyelitis virus grown on monkey kidney tissue, which leads to a good antibody response in human beings. At the time of writing, reports are available on only a few children given vaccine seven months earlier. In these the antibody levels were well-maintained. A booster effect was observed when vaccine was given to a subject who already had antibody from a previous natural infection [Salk (41)]. Milzer and co-workers (42) have reported obtaining a rise in antibodies in the majority of 30 adults from a vaccine combining all three types inactivated by ultraviolet light. The Salk vaccine is being used on an experimental scale on approximately 650,000 children between the ages of six to nine years, one-third being given placebos (43). The second approach is the development of modified or attenuated strains of virus which then can be given orally as live vaccines Many experimental technics are being employed. One approach has been to use rodent-adapted strains. Type II has long been rodent-adapted and recently adaptation of both Type I [Li & Schaeffer (44); Koprowski *et al.* (45)] and Type III [Li & Habel (46); Li & Schaeffer (44); Casals *et al.* (47)] viruses to rodents has been accomplished by using spinal cord inoculation of mice with material that had been passed many times in monkey cell tissue culture Such adapted viruses lost their pathogenicity for monkeys Koprowski *et al.* (48, 49) have used a modified Type II virus, the "TN" strain, for oral immunization of 81 children. They were successful in causing the development of specific antibodies in 70 without evidence of viremia or illness in any of them. Fourteen of these children were studied at intervals of up to three years later [Koprowski *et al.* (50)] and all showed a persistence of antibodies Koprowski *et al.* (51) have also fed mouse-adapted Type I to three individuals without producing illness or viremia, but succeeded in establishing the virus in the stool and provoking antibodies. On one patient the stool virus was found to be no more pathogenic for monkeys than the original strain Cox (52) has urged the advisability of a nonmammalian host for propagation of a vaccine He reports the successful adaptation of a Type II strain to eggs by Roca-Garcia *et al.* (53), Cabasso *et al* (54), and Moyer *et al* (55). Sabin (56) has found that strains of all three types can be produced in tissue culture, by rapid passage of large inocula which are avirulent for monkeys, although large doses of such strains give rise to antibodies when fed to cynomolgus monkeys.

Isolation and Identification

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test [Pollard *et al.* (60); Svedmyr *et al.* (61)].

the electronmicroscope that Type II poliomyelitis virus (MEFI strain) is a spherical particle measuring 27 mμ in diameter.

COXSACKIE VIRUSES

General.—Melnick & Curnen (1, Chap 14) fully described the state of knowledge about these viruses up to the end of 1951. The subject was reviewed in the middle of 1952 [Kilbourne (79); Huebner *et al.* (80)]. The latter present clear-cut evidence on the association of the clinical picture of herpangina with the presence of any of one of six different strains of Group A Coxsackie viruses in the throat or stools or both of the patients They point out that these strains were isolated from 85 per cent of patients with the disease, 60 and 40 per cent respectively from contacts in neighborhood or family, and only from 3 5 per cent of the noncontacts of the community at large. Infection only produced immunity to the given strain and repeated infections with different strains appear to occur in children, such infections causing symptoms of clinical illness more often than not Isolation of the virus was significantly more frequent from children under four years With increasing age, antibodies develop to an increasing number of strains It appears probable from serological surveys conducted by these authors and others that herpangina is one of the most widespread minor illnesses of childhood. These same authors summarize the evidence that strains of Group B virus are associated with epidemic pleurodynia

Epidemiology.—The numerous epidemiologic reports published since then have added very little to these two firmly established points However, careful studies by Johnsson (81) have emphasized the clinical spectrum of this group of diseases as they may occur in a family. He studied eight families, three with Group A infection and five with Group B. Insufficient data were available in the Group A families to allow any conclusion to be drawn. However, in the five Group B families comprising 23 persons, 11 of 13 children and 7 of 10 adults showed symptoms Aseptic meningitis occurred in eight children and one adult, with pleocytoses of from 14 to 108 cells per c mm. Pleurodynia occurred in two adults and myalgia occurred alone in the remaining four adults and one child, one adult and two children had myalgia complicating their aseptic meningitis, and there were two children with minor illnesses Type B_3 was isolated from the stools of eight sick children and one healthy child, and from three sick adults In two patients in one family virus was found in the feces nine and three days before onset of symptoms When the infection was introduced into the family, the symptomatology appeared to be related to the age of the individuals in the family, aseptic meningitis being more common in children and pleurodynia and myalgia more common in adults The incubation period was about five days

Clinical—The relationship of Coxsackie B virus to the aseptic meningitis syndrome has been further clarified by the isolation of the virus from the spinal fluid In 1952 Gabinus *et al* (82) reported the isolation of a Group B virus from one such case Recently Hummeler *et al* (83) have reported the

total of 243 cases in Belfast during the epidemic of 1950. The commonest symptoms were convulsions, fretfulness, and anorexia. Three infants died, and only one recovered completely. Neonatal poliomyelitis was included in the above reports. Four infants (13, 12, 10, 8 days postpartum) developed poliomyelitis in a private nursing home of 13 beds. Three of them died and one had paralysis of the left arm Poliomyelitis was known to be in the vicinity but the mothers were not clinically involved (69). Another case of poliomyelitis in a four-day old infant, born six weeks after his mother had had a mild attack of poliomyelitis, was reported by Johnson & Stimson (71). These reports indicate that the low reported incidence of neonatal poliomyelitis may be due to decreased exposure on the one hand and difficulty in diagnosis on the other, rather than a natural resistance on the part of individuals in this age group.

Miscellaneous.—Among other epidemiologic studies the following deserve mention: Sartwell (72) on the basis of statistical analysis calculates that the median incubation period for poliomyelitis is 12 days. Studies from Sweden emphasize the possibility of spread by means of contaminated water during an epidemic in Malmo in 1949 Poliomyelitis virus was isolated from water supplies with evidence of fecal pollution [Huss, Kling & Nantin (73)], and the overall incidence was greater, especially in the 0- to 2-year group, in the areas supplied by contaminated water than in areas with a better water supply [Heinertz & Vahlne (74)] A series of studies of various factors in the spread of poliomyelitis were reported from Hidalgo County, Texas. Paffenbarger & Watt (75) reported that fly-control measures which reduced the incidence of dysentery did not reduce the number of cases of poliomyelitis or affect the time of the epidemic. The major role in spread was person to person contact as indicated by an analysis of the attack rates Those among household contacts were 15.8 per 1000, among nonhousehold contacts were 5.4 per 1000, and among those with no known contacts were 0.7 per 1000. The conclusions concerning the relative unimportance of fly-spread disease were made despite the fact that Melnick & Dow (76), working among the same population, reported little difficulty in isolating virus from privies and from flies, despite exposure of the virus to air at high summer temperatures. Sabin (77) rightly emphasizes that probably all the known sources of poliomyelitis virus in nature play a greater or lesser role in the transmission of the disease, but the most important is spread from person to person by the fecal-oral route, with droplet infection from the oral pharynx playing little if any role Contaminated food or drink, whether by humans or flies, is an important mode of entry He emphasizes attention to cleanliness and avoidance of bodily contact rather than avoidance of those associations such as churches or movies in which infection by the air borne route is the major hazard

Structure of Virus

Electronmicroscopy.—Schwertd *et al* (78) have overcome the technical difficulties encountered by previous investigators, and have demonstrated in

Robertson (91); Anderson *et al.* (92)] This began in February, 1951 and continued through April of that year. There were 40 recognized cases in the Murray Valley and 17 deaths. The virus was isolated from the brains of two fatal cases, but all attempts at isolating the agent from patients before death failed. The virus was more easily isolated on the chorioallantoic membrane of the developing hen's egg, than in other laboratory hosts; after isolation it was found to cause encephalitis by intracerebral inoculation in three-week-old mice, and by both intracerebral inoculation and peripheral routes, in suckling mice; it also produced encephalitis in chickens, sheep, and a monkey, and a subclinical infection in rabbits and guinea pigs The virus is closely related to Japanese B virus. The clinical disease was most severe in infants, leading to considerable brain damage and a high mortality. Among older children and adults there were more milder cases. The onset tended to be abrupt with malaise, anorexia, headache, fever, lethargy and drowsiness, convulsions (especially in the infants) vomiting, giddiness and irritability. Consciousness became progressively impaired, more rapidly in the children Cervical rigidity was constant and pleocytosis occurred in the spinal fluid ranging up to about 400 cells per c mm. Of these the majority were lymphocytes although up to 40 per cent polymorphonuclear cells were encountered. As in other encephalitides the cerebrospinal fluid protein continued to rise after the acute phase, while the pleocytosis decreased. In the severe cases upper and lower neuron paresis developed, with inability to swallow and respiratory dysrhythmia. Pathological examination revealed widespread loss of neurons; disappearance of Purkinje cells of the cerebellum during the acute stage with little or no reaction, and areas of tissue necrosis in the white matter of the thalamus and cerebellar cortex. Microglial response occurred early with neuronophagia, and there was a less striking lymphocytic response.

A survey of the population of eastern Australia by serological methods revealed evidence of MVE (Murray Valley Encephalitis) to be widespread north of the Victorian great dividing range, in humans, horses and dogs. The main natural reservoir appeared to be in native and domestic birds among whom the infection is maintained by transmission via mites and mosquitoes from one nesting season to another A viremia of about three days duration is known to occur in the domestic fowl from which mosquitoes could carry the infection to man. The incidence of subclinical to clinical cases in the area of greatest intensity was 700 to 1. On epidemiologic and clinical grounds it is considered that MVE virus was the cause of Australian X disease described in 1917.

RESPIRATORY VIRUSES

INFLUENZA

Two recent studies, one on the antigenic structures of influenza virus [Jensen & Francis (93)] and the other on the predominant antibody pattern in the sera of the population at different ages [Davenport, Hennessy & Francis (94)] elaborate further on the relationship of different strains of the virus

isolation of Group B, Type 2 (Ohio) from one patient with stiff neck and back muscle tenderness. This patient was one of eleven so afflicted in an institution. This spinal fluid was examined on the fifth day of illness and the isolation procedures carried out four times. Spinal fluids on three other patients examined on the sixth, eleventh, and fourteenth day after onset were negative. Hummeler (84) has also isolated Group B, Type 3 from the spinal fluid of a sporadic case of aseptic meningitis in an infant. A contribution to the pathology of this disease in human beings has been made by Lepine *et al* (85) who described the microscopic picture of muscle taken by biopsy from two patients suffering from Bornholm's disease during an epidemic in Brittany. The muscle of one case showed focal infiltration of mononuclear with some polymorphonuclear cells. There was hyaline degeneration of muscle fibers with loss of striation. This was followed by atrophy and replacement of muscle bundles by an eosinophilic hyaline mass The picture was entirely similar to that induced in suckling mice by Group B viruses In the second case the muscle was less involved, showing only focal infiltration of the muscle septums. Viruses were isolated both from the muscle biposy specimens and from the stools of both patients *These findings suggest that the symptomatology* is initiated by actual invasion of the muscles by the virus.

Poliomyelitis and Coxsackie.—The relationship between these viruses has been confusing. However, the present concept appears to be that, when both viruses are found together, such a finding is coincidental and there is no evidence either for interference between the two viruses or potentiation of the poliomyelitis viruses by the Coxsackie viruses.

Classification —The problem of classification of these viruses remains unsolved. Melnick (86) points out the difficulty of classifying the two groups on the basis of the pathologic effects induced in suckling mice, as originally suggested by Dalldorf & Sickles [see 1, Chap. 14 or *Science*, 108, 61 (1948)]. In this classification Group A caused generalized myopathy without central nervous system or other lesions, and Group B focal myopathy together with lesions in the central nervous system, fat, and viscera However, in reality, graded effects can be demonstrated from Conn-5 type, which produces severe damage to fat, liver, and pancreas with variable muscle damage, to Texas Type I, which causes severe muscle and cardiac damage and rare central nervous system, fat or visceral lesions. Despite these objections this broad classification continues to be useful to the clinician Serologically 16 different antigenic types have already been described, of which four are associated with Group B. All of the latter have been isolated from patients with the pleurodynia syndrome [Contreras *et al* (87)] The introduction of tissue culture technics promises to simplify the isolation and classification of Group B viruses, although the classification of the Group A viruses still remains complex.

MURRAY VALLEY ENCEPHALITIS

An important study of an epidemic of severe encephalitis comes from Australia [Anderson (88); French (89); Robertson & McLorinan (90);

epithelium in animals appears to be at variance with the absence of such destruction of infected entodermal cells of the allantoic membrane of the developing hen's egg. Henle *et al.* (96) have recently demonstrated that these cells are capable of continued production of virus for over 30 hr. without histological evidence of any damage. However, necrosis of cells does appear eventually [Eddy & Wyckoff (97)]. Electronmicroscope studies have shown that influenza virus multiplies on or close to the surface of the cell, producing long filaments which become pinched off into the spherical particles characteristic of the virus [Hoyle (98); Murphy & Bang (99); Wyckoff (100)]

Common Cold

A most important achievement is that of Andrewes and his colleagues (101) who reported their success in growing this virus in human embryo lung. These workers inoculated nasal secretions from a patient with a cold onto human embryo lung in tissue culture They then were able to cause typical colds with intranasal inoculations into normal volunteers of material from the tenth subculture This made an estimated dilution of the original nasal washings of 100,000 fold and, since in their previous extensive experience they had been unable to induce a cold with a dilution of washings of more than 1,000 fold, they concluded that the virus had multiplied in the tissue culture. From one of the culture-induced colds it was possible to pass the virus successfully to one of six volunteers Confirmation and extension of this work will be eagerly awaited as a number of previous attempts to cultivate this virus in other than human hosts have eventually resulted in failure.

PRIMARY ATYPICAL PNEUMONIA (PAP) AND ACUTE RESPIRATORY DISEASE (ARD)

New viruses —Hillman *et al.* (102), during an epidemic of influenza A prime, isolated an agent from the throat washings of patients with PAP and ARD that was cytopathogenic for HeLa cells but did not grow in any of the common laboratory hosts. The patients appeared at the beginning and towards the end of the influenza epidemic. They developed both complement-fixing and neutralizing antibodies against this agent. Such antibodies were also found to develop among other patients with PAP or ARD and to be present in both the acute and convalescent sera of certain patients with proven influenza. This agent was found to be identical with the agent that produces degeneration in tissue cultures of human adenoids [Rowe *et al.* (103)]. This latter, referred to as the "AD" agent, is filterable; it does not grow in nonliving media, nor does it produce disease in experimental animals, but does grow in tissue cultures of various sorts of cells including HeLa. It is neutralized by human gamma globulin in dilution of 1:500 It seems probable that the application of tissue culture techniques may make possible a more detailed classification of respiratory infections

Canine distemper —It has long been recognized that primary atypical pneumonia is probably a disease of multiple etiologies. The virus of canine

and suggest a concept of the epidemiology of this disease. The former study of of Type A virus indicates that this virus possesses a number of antigens, at least 18, that are shared by many strains and that strain differences are due to the predominance of certain antigenic components. The authors suggest that the appearance of a strain with completely unrelated antigens or the complete disappearance of old antigens is unlikely. The importance of this concept is that it supports the possibility of adequate prophylaxis by the incorporation into a vaccine of several strains with varied antigenic components so that the vaccine contains an antigenic mass in which all known components are adequately represented. The latter study is a corollary of the former. In it the authors describe the predominant antibody pattern in the sera of individuals of different ages. They found that the dominant antibody pattern in any age group represented a specific reaction to the strain currently prevalent when those individuals were children For example, antibodies against the recent A prime strain were high in groups under 12 years and then declined until at 20 years they were almost unmeasurable. From the age of 12 years antibodies against PR 8 and the older Type A strains appeared whereas in the groups over 28 years old antibodies for swine influenza were detectable for the first time This observation supported the previous suggestions that the 1918 pandemic of influenza was due to a strain in which the predominant antigenic component was the same as or closely related to that of swine influenza The same general concept holds true for Type B. Type C antibodies were found in high titer fairly evenly distributed at all ages Presumably this virus is common in infancy and encountered frequently throughout life without causing symptoms It would appear from this study that the initial infections that occur predominantly in childhood have an effect on the antibody production mechanism which persists through life Thus the antibody to the original infection is boosted even by infection with new strains since these also possess minor antigens that are specific for the original strain as well as their own predominant antigens These predominant antigens in turn lead to development of specific antibodies against themselves This process results in a broader antibody pattern among older age groups which can be correlated with the decreasing incidence of the disease with increasing age By such population surveys it is possible to reconstruct the antigenic history of influenza virus, and this may throw light on the problem of the cycles of influenzal epidemics.

Verlinde & Makstenieks (95) have investigated the mechanism of the clinically recognized synergism between influenza virus and bacteria, particularly in recent years the staphylococcus When a monkey was inoculated with influenza A virus alone, necrosis and desquamation of the epithelium, mainly of the bronchioles, occurred accompanied by peribronchiolar and interalveolar edema. Staphylococci alone led to slight bronchiolitis without necrosis, while a combination of the two led to epithelial necrosis involving the whole of the respiratory tract, bronchiolitis, and bronchopneumonia.

The well-recognized necrotizing effect of influenza virus on respiratory

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Canine distemper.—It has long been recognized that primary atypical pneumonia is probably a disease of multiple etiologies The virus of canine

distemper may prove to be one such. Adams (104) gives suggestive evidence that some cases of atypical pneumonitis may be caused by this virus. He emphasizes the similarity of the pathologic picture in the lungs of humans dying of penumonitis to those of ferrets, dogs, and monkeys suffering from distemper. The lining of the bronchioles shows proliferation and destruction of the epithelium; the formation of giant cells and cells with one or two (bipolar) cytoplasmic inclusion bodies occur in both diseases In two of his patients with atypical pneumonia he was apparently able to demonstrate a slight rise in neutralizing antibodies against the distemper virus. He also pointed out that distemper may be a common infection of man since it appears to be neutralized by human gamma globulin. This "inclusion body" pneumonitis has previously been described as a separate clinical entity which has occurred in epidemic form and been attended by a high mortality among prematures. It is obviously important to extend the above observations since, if confirmed, they may influence our prophylactic measures against this infection.

PSITTACOSIS

This disease has long been known as an occupational hazard to those engaged in the poultry business. However, a marked increase was noted both in the United States and England when interstate transport or importation of psittacine birds was permitted Westwood (105) reported that within two months of lifting the ban on importation of these birds into England, a series of outbreaks of the disease occurred The ban has since been reimposed with again a decrease in the disease to occasional sporadic cases. In the United States the high incidence continues [Sigel (106)]. The greater hazard of the psittacine birds over the many other species known to harbor the virus appears to be the more intimate contact that these pet birds have with humans Especially is this intimate contact important when the birds are sick, at which time they excrete large amounts of virus

HERPES VIRUS GROUP

HERPES SIMPLEX

Neonatal infection —The importance of this virus as a potentially serious danger in childhood has been emphasized by the appearance of several reports of fatal infection of the newborn. Quilligan & Wilson (107), Zuelzer & Stuhlberg (108), Florman & Mindlin (109), Pugh *et al.* (110), and Epstein & Crouch (111) have each described one to eight cases. The infants usually become ill on about the fifth to seventh day of life and may show a vesicular eruption of the skin or mucous membranes, including the conjunctiva The vesicular eruption may be minimal, however, and the disease manifest itself by such nonspecific signs as fever or hypothermia, lethargy, icterus, at times hepato- and splenomegaly, vomiting, respiratory distress, cyanosis, or circulatory collapse. They may suffer a terminal septicemia from *Pseudomonas aeruginosa*. At autopsy areas of necrosis were found especially in the liver,

although the lungs, adrenals, and central nervous system were often involved. Characteristic intranuclear inclusion bodies were found in the vicinity of the necrotic areas. Herpes virus was isolated from the liver in one of Zuelzer's cases and in Pugh's case, and from the skin lesions of Florman's case. In Florman's case recovery took place although there were severe neurologic sequelae and chorioretinitis. An analysis of the reported cases indicates that in those in which the mother was known to have antibodies against herpes the victims were very small prematures. In two other instances the mother had an acute illness compatible with a primary herpetic infection about the time the infant was born. The remaining cases, one must assume, were offspring of uninfected mothers, who were infected by contacts in the newborn nursery. With increasing improvement in hygiene among the population, with accompanying decrease in the spread of the herpes virus in infancy, it is to be expected that an increasing number of infants will be born who are susceptible. The explanation for the occurrence of the disease in the very small premature offspring of an immune mother may be that these infants were born too early in gestation for maternal antibodies to have passed the placental barrier. Actual information on this point is still lacking

Natural history.—Buddingh *et al.* (112) have shed light on the natural history of herpes infection in childhood. They point out that within four to seven days after a primary herpetic infection antibodies develop. However, in individual patients after varying intervals of time the particular level of antibody reached by an individual is not maintained but drops to relatively low levels only to be boosted again by subclinical infection This is in contrast to the findings in the few adults studied in whom the antibody titer is maintained over periods of months. Similar observations have been made by Jawetz & Coleman (113). The existence of the subclinical carrier as an agent for the transmission of the disease is also clearly shown by Buddingh *et al.* (112) in that they demonstrated herpes virus in the saliva of 20 per cent of 72 healthy children from 7 to 24 months of age, of 9 per cent of 199 from 3 to 14 years, and of 2.5 per cent of 185 adults.

During the period under review considerable attention has been paid to some of the problems of the multiplication of the virus. The pattern of the development of the virus on the chorioallantoic membrane, has been described by Scott *et al* (114) They showed that the infectious virus disappeared for about 6 to 8 hr. and then reappeared in an increasing amount. This pattern of virus growth followed that first detected in the *E coli* bacteriophages which was later described also for several animal viruses The actual site of multiplication has been investigated by several workers Francis & Kurtz (115) and later Ackerman & Kurtz (116) produced evidence in favor of multiplication of the virus in the cytoplasm of the cell, particularly in relation to the mitochondria. However, the electronmicroscopic pictures of Morgan *et al.* (117) show clearly the infected nuclei containing virus particles of varying size These consist of dense particles (30 to 40 mμ), those less dense (40 to 60 mμ), and particles with an outer membrane (70 to 100 mμ) The nu-

clear membrane ruptures, liberating the single membrane particles into the cytoplasm where they acquire a double membrane (120 to 130 mμ). The evidence presented by Scott *et al.* (118) on the sequential changes that occur in the nucleus during the early hours after inoculation of the virus onto tissue cultures of rabbit corneal cells and that of Gray & Scott (119) on the association of virus with the nuclear fraction of liver cells of herpes-infected chick embryos favor the concept that the early stages at least of the virus development take place in the nucleus and that the well-known inclusion bodies at one stage of their evolution represent aggregates of virus particles. The clarification of the cell virus relationship in this infection requires further investigation.

Varicella-Zoster

Cultivation.—An important advance in our understanding of this virus (or viruses) has been achieved by Weller & Stoddard (120) and Weller (121) who have reported the serial propagation of cytopathogenic agents from cases of both varicella and zoster in tissue culture of human embryo skin and muscle, or of foreskin. Each of these cytopathogenic agents grew in a similar way, spreading slowly from an infected cell in a centrifugal manner. The infected cells had the characteristic intranuclear inclusion bodies. No virus could be obtained from the supernatant fluid, and the agent could only be passed by lightly grinding the cells of the original culture and seeding this suspension into a new culture. Although not containing the virus, the culture fluids contained a complement-fixing antigen which reacted with the serum of a patient recovered from varicella. It seems probable that Weller's technic will provide the tools with which to unravel the true relationship between varicella and herpes zoster.

Pathology.—Cheatham (122) reports the pathological findings in a woman of 50 with Hodgkin's disease. She developed acute abdominal pain and, six days later, the rash of bilateral herpes zoster of the trunk, and finally a generalized vesicular eruption. She died on the eighteenth day of her disease. Type A inclusion bodies were found in the skin lesions, and in many foci of necrosis in myocardium, pancreas, adrenals, and one ovary. An ulcer had developed in a necrotic area in the esophagus in which inclusions were also found. In the posterior root ganglia massive hemorrhage and necrosis had occurred as in the textbook descriptions. However, for the first time definite inclusion bodies were seen in ganglion cells, the absence of which was specifically noted by Denny-Brown *et al.* (123) in their cases. Similar changes were found in the sympathetic ganglia, in the neurilemma cells of the nerve twigs in the corium, and throughout the myenteric plexus of the stomach. The observer noted that the lesions in the nerve plexuses of the esophagus and stomach were accompanied by a cellular infiltration which was absent from the nervous lesions elsewhere. Since the patient had been treated with nitrogen mustard between the time of the abdominal pain and the development of the rash, he argues that the visceral lesions were early and that the

spread of the virus was along the white rami of the sympathetic nerves to the posterior root ganglia and thence centrifugally to the skin. These findings present the most cogent evidence so far available bearing on the controversial issue concerning whether the zoster virus travels centrifugally to the skin from the central nervous system or vice versa. He considers the visceral foci to be neurogenic rather than hematogenous, and suggests that the spread of the virus is hematogenous in the totally susceptible individual (varicella) and neurogenic in the partially immune (zoster).

POX VIRUSES

Variola

Diagnosis.—The early diagnosis of small pox has become refined and readily available in special laboratories. The methods are summarized by MacCallum (124) as follows: (*a*) Scrapings are made from skin lesions and the slides are stained for elementary bodies. A presumptive diagnosis can be given in about one hour after receipt of the slides. (*b*) A complement fixation test is performed, using material from the skin, or from the blood in the first few days of the illness as antigen. A diagnosis can be given in 24 hr. after receipt of the material (*c*) Cultures of vesicular fluid or crusts are made on the chorioallantoic membrane of the embryonated hen's egg. This is the most sensitive test, the virus causing small characteristic pocks in 72 hr. which can readily be distinguished from those caused by vaccinia virus, but may be mistaken for those due to herpes simplex virus. The virus of chicken pox causes no lesions

Virus isolation.—Downie *et al.* (125) have isolated the virus from the blood of 3 of 25 patients who ultimately recovered during the first two days of their illness, and of 11 of 14 patients who ultimately died In the latter group the virus was isolated even up to the eighth day of the illness. The persistence of viremia beyond the second day appears to have a bad prognostic implication The isolation of the virus has its greatest public health application in toxic or hemorrhagic cases who may die before the typical eruption occurs Verlinde & Van Tongeren (126) have reported finding the virus in the nasopharyngeal secretions of 2 out of 13 cases tested. One was a woman who was revaccinated the day following exposure and 17 days later developed symptoms, without a rash, which lasted for two days. Virus was isolated from throat washings three days before her symptoms appeared. The second isolation was from the throat washing of an unvaccinated eighteen-year-old girl on the eighteenth day after contact This carrier did not become ill but had antibodies one month later which were presumed to be due to this contact These findings emphasize the possibility of relatively asymptomatic carriers in the spread of the disease.

Pathology.—Bras (127) has redescribed the pathology of small pox as seen in Indonesia Since antibiotics were used in the majority of patients, interference by the effects of secondary bacterial infections was avoided. He

clear membrane ruptures, liberating the single membrane particles into the cytoplasm where they acquire a double membrane (120 to 130 mμ). The evidence presented by Scott *et al.* (118) on the sequential changes that occur in the nucleus during the early hours after inoculation of the virus onto tissue cultures of rabbit corneal cells and that of Gray & Scott (119) on the association of virus with the nuclear fraction of liver cells of herpes-infected chick embryos favor the concept that the early stages at least of the virus development take place in the nucleus and that the well-known inclusion bodies at one stage of their evolution represent aggregates of virus particles The clarification of the cell virus relationship in this infection requires further investigation

VARICELLA-ZOSTER

Cultivation.—An important advance in our understanding of this virus (or viruses) has been achieved by Weller & Stoddard (120) and Weller (121) who have reported the serial propagation of cytopathogenic agents from cases of both varicella and zoster in tissue culture of human embryo skin and muscle, or of foreskin Each of these cytopathogenic agents grew in a similar way, spreading slowly from an infected cell in a centrifugal manner. The infected cells had the characteristic intranuclear inclusion bodies No virus could be obtained from the supernatant fluid, and the agent could only be passed by lightly grinding the cells of the original culture and seeding this suspension into a new culture. Although not containing the virus, the culture fluids contained a complement-fixing antigen which reacted with the serum of a patient recovered from varicella It seems probable that Weller's technic will provide the tools with which to unravel the true relationship between varicella and herpes zoster

Pathology.—Cheatham (122) reports the pathological findings in a woman of 50 with Hodgkin's disease She developed acute abdominal pain and, six days later, the rash of bilateral herpes zoster of the trunk, and finally a generalized vesicular eruption She died on the eighteenth day of her disease Type A inclusion bodies were found in the skin lesions, and in many foci of necrosis in myocardium, pancreas, adrenals, and one ovary. An ulcer had developed in a necrotic area in the esophagus in which inclusions were also found. In the posterior root ganglia massive hemorrhage and necrosis had occurred as in the textbook descriptions. However, for the first time definite inclusion bodies were seen in ganglion cells, the absence of which was specifically noted by Denny-Brown *et al* (123) in their cases Similar changes were found in the sympathetic ganglia, in the neurilemma cells of the nerve twigs in the corium, and throughout the myenteric plexus of the stomach. The observer noted that the lesions in the nerve plexuses of the esophagus and stomach were accompanied by a cellular infiltration which was absent from the nervous lesions elsewhere. Since the patient had been treated with nitrogen mustard between the time of the abdominal pain and the development of the rash, he argues that the visceral lesions were early and that the

spread of the virus was along the white rami of the sympathetic nerves to the posterior root ganglia and thence centrifugally to the skin. These findings present the most cogent evidence so far available bearing on the controversial issue concerning whether the zoster virus travels centrifugally to the skin from the central nervous system or vice versa. He considers the visceral foci to be neurogenic rather than hematogenous, and suggests that the spread of the virus is hematogenous in the totally susceptible individual (varicella) and neurogenic in the partially immune (zoster).

POX VIRUSES

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found no case of osteomyelitis in this series although it was described in the earlier literature (see below under vaccinia). He emphasizes that the early lesion is in the walls of the capillaries in the corium. Following this, degeneration occurs in the adjoining epidermal cells leading to swelling and liquefaction which is the basis for the vesicle. The same author (128) in an attempt to explain the prevalence of scarring on the face, as opposed to other parts of the body, studied sections of skin from face and thigh in 177 cases He demonstrated that degeneration and necrosis occurred particularly in the sebaceous glands which are many times more numerous in the skin of the face than elsewhere.

VACCINIA

Vaccination.—Problems of interpretation of immune and vaccinoid responses still merit attention in relation to maintaining immunity to small pox. Benenson *et al.* (129) compared the results of the reaction to potent and heat-killed vaccines in a group of well-vaccinated Army officers. They pointed out that sensitization to the protein in killed vaccine may be great enough to lead to a papule by 24 hours and a vesicle by 48 hours, with subsidence of the lesion and scab formation by the eighth day. This could easily be mistaken for a vaccinoid reaction indicating partial immunity. The incidence of sensitivity reactions of this extent is illustrated by the results observed by these same authors in a class of medical students Among the one-half of the class vaccinated with dead vaccine, vesiculation occurred in 29 per cent, 82 per cent vaccinated with live vaccine developed vesiculation due to the virus infection The significant difference between sensitivity and a true vaccinoid reaction is the time of development of maximum skin involvement. In a true vaccinoid reaction the maximum erythema does not occur until after the third day. This differentiation is important since no boost in immunity can be expected from dead vaccine although evidence of sensitization indicates previous vaccination but not coincident immunity.

Vaccinia gangrenosa.—An unusual and very serious complication has been described by four groups of authors as vaccinia gangrenosa or prolonged generalized vaccinia [Bigler *et al.* (130); Laurance *et al* (131), Keidan *et al.* (132); Barbero *et al.* (133)]. This consisted of a failure of the primary vaccination to heal. In each case the lesion grew larger, spread as an ulcerating lesion locally, and, in addition, metastasized to other areas of the skin, viscera, and bone. Death occurred after a prolonged illness of many weeks or months in all except Barbero's case in which healing took place following the administration of hyperimmune vaccinia gamma globulin developed by Kempe (133). A careful pathological study of the patient described by Laurance *et al.* (131) was made by Hall *et al* (134). They found necrotic foci in the lungs, adrenal, kidney, and pancreas, but no inclusion bodies were found in these organs or in the skin. Vaccine virus was recovered from skin, serum, liver, spleen, and marrow. The case described by Barbero *et al.* (133) is significant as being the only documented recovery from this complication. This five-

year-old white boy was seen four months after primary vaccination with extensive ulceration of his left shoulder and metastatic ulcers on his scalp and left forearm. He had clinical and x-ray evidence of a low grade osteomyelitis of his fourth right metacarpal bone. Vaccine virus was recovered from his skin and from scrapings of the affected bone which were bacteriologically sterile Inclusion bodies were also found in both. Healing began immediately after the first dose of 7½ ml. of anti-vaccinial gamma globulin. He was given four further doses of 10 ml. each at two-weekly intervals. Virus was detectable in the lesions until after the fourth dose The area was completely healed by the end of four months after the first dose. It is worthy of comment that this patient presents definite evidence that an osteomyelitis may be caused by a virus. The bloods of two of the patients were tested for the presence of gamma globulin. One was found to have agammaglobulinemia [Keidan *et al.* (132)] but in the other the gamma globulin was normal [Barbero *et al.* (133)]. However, no antibodies against vaccinia virus were detected in any of the patients tested [Hayles *et al.* (135)]. They pointed out that patients with known agammaglobulinemia have been vaccinated successfully. The role of this clinical abnormality of the blood, associated as it is with recurrent bacterial infections of a serious nature, requires further exploration in relation to antibody formation in general

Fetal vaccinia.—McDonald & MacArthur (136) report a case of fetal vaccinia in a premature infant who lived 15 hr. The mother was vaccinated three months previously at the third month of pregnancy. She had a severe reaction and could not work for two to three days. The skin was widely covered with sodden white umbilicated necrotic lesions At autopsy necrotic foci were found in many organs; in the lungs several necrotic areas with early calcification were present. Inclusion bodies were found in both skin and lungs. Since the pathological lesions were of long duration, it would seem probable that this fetus was infected at the time of the mother's vaccination from the accompanying viremia. This appears to be an extremely rare accident of vaccination

HEPATITIS

The problems of this wide-spread disease have been very fully reviewed by MacCallum *et al.* (137), Gellis & Hsia (138), and Neefe (139).

Infectious Hepatitis

Cultivation of virus—Certain preliminary reports on the cultivation of the virus of infectious hepatitis (IH) in the embryonated hen's egg were mentioned in the 1951 review by Burnet (2) and by Havens & Paul (1, Chap. 15) The isolation of two strains of this agent was described by Henle *et al.* (140) who pointed out that their findings were compatible with the

83 per cent of the volunteers. These results differed from their experience when using the natural viruses in volunteers, since 31 per cent of the latter became jaundiced out of a total infection rate of 75 per cent. The incubation periods of the disease caused by the culture virus were similar to those found with the natural virus. Recently Mirick *et al.* (142) have repeated these experiments with later tissue culture strains and induced similar though less severe illness in volunteers who, however, were not immune to subsequent infection with "natural virus" The preliminary report of Henle *et al.* (140) indicated that the few volunteers infected by them with an earlier tissue culture passage did become immune. Further work is required to clarify these relationships. The development of a skin test for the detection of those immune to infectious hepatitis, using irradiated infected amniotic fluid, was reported by Henle *et al* (143) in 1950. Technical difficulties of maintaining stability of the material, have prevented its general use. When potent lots of the material were available (as tested in volunteers for infectivity before irradiation) it could be shown to be positive in a high percentage of known recovered patients. For example, Knight *et al* (144) showed 88 per cent positive tests among 42 convalescents in an epidemic in Missouri, as opposed to 15 per cent among a number of uninfected persons. Bennett *et al* (145) found a high correlation between positive tests and infection among both nurses and children in an institutional outbreak. Disappointment has been experienced however with other lots [Gellis & Hsia (138)]

Epidemiology.—The importance of anicteric cases in the epidemiology of the disease is becoming more widely recognized. Knight *et al* (144) found enlarged livers in 10.4 per cent of 134 children in an epidemic area, and 64 per cent of these had abnormal cephalin-cholesterol flocculation tests without ever developing jaundice. Denber & Leibowitz (146) report on 30 sporadic cases with anicteric hepatitis diagnosed by the presence of abnormal liver function tests Patients had symptoms of fatigue, anorexia, distaste for smoking, abdominal pain, headache, and nausea; 79 per cent had tenderness over the liver but none had jaundice. Thorling (147) describes an outbreak of hepatitis in a bakery in which 7 of 41 persons became ill, six with and one without jaundice, while five of the remaining 34 "healthy" persons had abnormal liver function studies but remained at work with minimal or no symptoms The importance of these anicteric cases as potent sources of infection is obvious Such cases occur especially frequently among infants where they create a hazard to the nursing staff. Capps *et al.* (148) and Bennett *et al* (145) describe an epidemic of infectious hepatitis in an orphanage for children of less than three years of age Over a period of eight years, 72 nurses and three other adults were involved. By careful observation and the use of liver function studies 42 children were diagnosed as having hepatitis; only one had hyperbilirubinemia. Among the common symptoms were loose stools, lassitude, anorexia, low grade fever, and failure to gain. The liver was usually enlarged, and returned toward normal with clinical convalescence. An incubation of as short as 11 days is recorded by these authors, and an 80 per cent

infection rate among the children. While excretion of virus in the stools is usually present for only a short time, Stokes *et al.* (149) have produced evidence that patients with "chronic active hepatitis" without jaundice may be chronic fecal carriers. The stools of two children, one 28 months old and one 11 months old, each of whom was observed with symptoms of hepatitis for over a year, caused jaundice when fed to volunteers. The stools were collected approximately 4 months and 15 months, respectively, after the onset of their acute disease. In contrast to the anicteric cases it is well to remember that prolonged jaundice in the newborn period may be due to viral hepatitis. The type of virus is obviously not diagnosable as a rule. One case of proven serum hepatitis is reported [Stokes *et al.* (149, 150)]. Among 156 cases of prolonged obstructive jaundice in infancy Hsia *et al.* (151) found four due to hepatitis as diagnosed by biopsy in three cases and abnormal flocculation tests in one. Craig & Landing (152) found 20 cases among 70 liver biopsy and 103 autopsy specimens over a ten-year period. Although rare, this diagnosis must be considered as a differential to that of congenital atresia of the bile ducts since surgery is tolerated very poorly by these infants This differential diagnosis is difficult since the liver function tests, so helpful in adults and older children, are not reliable in this age agroup [Weller (153); Hsia & Gellis (154)]

Prophylaxis.—The value of gamma globulin as a prophylactic measure, in doses as small as 0 01 ml. per lb of body weight, has been amply confirmed [Brooks *et al* (155)] Drake & Ming (156), in a controlled study during an epidemic in an institution for mental defectives, showed that the main effect was to decrease the incidence of clinical disease. Among individuals injected with either 0 005 ml of gamma globulin per lb. or 0 01 ml. per lb, approximately 40 per cent developed hepatitis as judged by three coincidental abnormal liver function tests but only 3 or 4 per cent respectively were icteric, whereas among the unprotected controls approximately 50 per cent became infected as judged by the same criteria, and of these approximately 30 per cent were icteric This study would seem to prove what was hypothesized on epidemiologic grounds [Stokes *et al.* (157)], that the mechanism for the development of permanent immunity in a closed institution following gamma globulin administration is the development of a subclinical infection. This is more clearly brought out by an analysis of the two "protected" groups Of those given 0 005 ml per lb gamma globulin no cases of "laboratory" hepatitis were observed after the eighth week, whereas, among those receiving 0 01 ml per lb, cases continued to occur up to the thirteenth or fourteenth week as they did among the controls. Three of six individuals who had been isolated in the hospital for amebiasis for six to seven weeks following their injection of 0 01 ml per lb. of gamma globulin developed jaundice approximately one month after being returned to the infected environment It would seem as if gamma globulin in doses of 0 005 ml. per lb. did not prevent the development of a mild immunizing infection, whereas a certain number of patients were completely protected by 0 01 ml per lb.

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5¼ years after his first blood donation had given rise to hepatitis in a recipient. The second was a woman who transmitted hepatitis to her infant son transplacentally. Her blood was infectious for volunteers on two occasions two years apart. She was symptomless and had no laboratory evidence of liver disease. The third was a man of 39 years who had a persistent viremia as tested in volunteers for 10 months at least, but was without symptoms although he showed abnormalities in his liver function tests. It must be remembered that not only serum hepatitis (SH) but also infectious hepatitis (IH) virus can be transmitted by transfusion if the blood happens to be taken shortly before the onset of jaundice or from an anicteric patient suffering from the latter disease [Neefe *et al.* (162)]. The resulting illness in the recipient will depend on the state of immunity present. If both viruses are present and the recipient has no immunity, then it is possible for the recipient to have a short incubation jaundice from the IH virus followed by a long incubation attack by the SH virus [MacCallum (164)].

Sterilization of blood products.—In view of these risks, considerable attention has been directed toward finding methods of sterilizing blood plasma. It had been reported earlier that ultraviolet irradiation of plasma was effective in destroying the virus of hepatitis without significantly altering the protein structure of the plasma However, recent reports, quoted by Albrecht *et al.* (159), have indicated that such a procedure is not universally effective. Several studies have been carried out by Murray *et al.* (165, 166) using volunteers to test the effectiveness of the various measures employed. They found that storage of infected plasma at room temperature between 70 and 74° F. for six months markedly reduced the infectivity and virulence of the virus, whereas, after storage for only three months under the same circumstances, the plasma still caused infection of three out of five volunteers The authors lay stress on the fact that the volunteers were challenged with only 1 to 2 ml. of plasma whereas a patient might well receive 500 ml. or more They point out that other materials derived from blood were in their experience innocuous in the amounts used experimentally, but were infectious in doses used clinically. Secondly, they tested the effectiveness of the three ultraviolet irradiation methods commonly used for sterilizing plasma. They found that they were unable to sterilize plasma completely by one irradiation by any method, although the virus did appear to be attenuated Using the Habel-Sockrider apparatus they irradiated the plasma five times and found complete sterilization as tested in volunteers, but also found the serum proteins had been altered by the process. Whether an intermediate test would have been effective in maintaining the integrity of the plasma proteins and while achieving complete sterilization remains to be seen. At the moment there is no satisfactory method available [illegible]

tients receiving human albumin intravenously However, Lesses & Hamolsky

doses for a period of time so that mild immunizing infection did not appear until later when passively acquired antibodies had fallen to a low enough level. The acute infections that occurred among the isolated individuals when they were again exposed indicates that the protective effect of gamma globulin had been dissipated by the end of seven to eight weeks.

Serum Hepatitis

Transmission.—In these days of wide-spread use of transfusion of blood and plasma the menace of transmission of hepatitis is always present. Some information on the risk of this accident has been gathered by several groups of workers. Murphy & Workman (158) reported an incidence in the United States of 12.8 per cent among those receiving commercially prepared plasma even though irradiated, whereas the risk from a single blood transfusion was from 0 5 to 1.5 per cent. Albrecht *et al* (159) reported an incidence of 7.6 per cent among 131 recipients of irradiated plasma in New York State. Madsen (160) reporting from Denmark found the risk to be about 1.0 per cent from a single blood transfusion while from pools of dried serum derived from 100 donors it was 3 to 4 per cent. There appears to be a direct correlation of the risk of jaundice with the size of the donor pools since the virus is highly infectious, as little as 0 00001 ml of infectious material being capable of causing the disease [Drake *et al.* (161)]. Neefe (139), on the basis of a routine application of a battery of liver function tests to all blood donors, estimated a carrier rate in the population of about 10 per cent Neefe *et al.* (162) and Murray *et al.* (163) present a detailed study of 8 donors of a group of 22 who were known to have given jaundice to recipients Six of the eight had at least one significantly abnormal liver function test. The blood of six of the eight was tested for presence of virus by inoculation into volunteers. Five of the six transmitted the disease, including one whose liver function tests were not significantly abnormal Liver biopsy was performed in four of the six whose blood was proven to contain virus. In two there was slight evidence of involvement such as round cell infiltration and connective tissue proliferation One of these was the donor whose liver function tests were not abnormal. In one other the histological evidence of involvement was questionable, and in the fourth there were gross signs of scarring and nodular regeneration. It appears from this study that the infectious donor may have no objective laboratory evidence of liver involvement, but more than likely will show some abnormality if enough tests are done Stokes *et al* (149) present details of the evidence for the statement previously reported (1) that the virus could be carried in the blood for as long as five years in an asymptomatic patient who had never had recognizable jaundice. These authors report the transmission of the disease to volunteers from three persons all previously known to have given jaundice to persons receiving their blood The first was the man referred to above, 44 years of age with periportal cirrhosis and abnormal liver function tests; virus was still present in his blood as tested in volunteers

and was immunologically distinct from the "epidemic" agent just mentioned. The patient developed neutralizing and complement fixing antibodies against his own virus, but not against the "epidemic" virus.

Behçet's disease.—Sezer (175) describes the isolation of an agent from three patients suffering from Behçet's disease. This disease is characterized by recurrent attacks of iridocyclitis with hypopyon and aphthous ulcers of the mouth and genitalia. Vitreous and subconjunctival serous fluids were inoculated onto the chorioallantoic membrane of the embryonated hen's egg. Pocks developed which could be passed in series and caused encephalitis in mice. Complement fixing antibodies were detected in the blood of 11 of 12 patients with Behçet's disease, using antigens derived either from allantoic fluid or from mouse brain, but were not present in the blood of five patients with iridocyclitis of other types, or of six normal individuals, three of whom had a positive Wassermann. Neutralizing antibodies were also demonstrated in one of the patients. The agent was clearly differentiated from herpes simplex, lymphocytic choriomeningitis, and Theiler's virus. It was filterable through a Seitz filter, and the electronmicroscope revealed many uniform particles It is hoped that this work will be followed up further by Sezer and others in order to clarify this puzzling disease

Aseptic meningitis—From Australia comes the report by Miles *et al.* (176) of the isolation of an agent in cortisone treated mice from the brain of a patient suffering from aseptic meningitis during an epidemic in Port Augusta, South Australia. From the cortisone treated mice it could be adapted to untreated mice, and to the yolk sac of embryonated hen's eggs; in guinea pigs it caused meningitis and myositis Rabbits and monkeys suffered subclinical infections It resembled a virus of the psittacosis group in appearance and measured 300 to 400 mμ by filtration technics No immunologic relationship could be established with mumps, psittacosis, or lymphocytic choriomeningitis. It gave rise to no neutralizing antibodies in either experimental animals or human beings Slight rises in the titers of complement fixing antibodies were found in four of the patients involved in the epidemic and in some, but not in most, of the patients suffering from aseptic meningitis in other parts of Australia. Perhaps further investigation will clarify the status of this agent and decide whether it will be one more etiologic agent that must be tested for routinely in patients with aseptic meningitis

West Nile virus.—Further information has been collected concerning the clinical picture produced by the West Nile virus From several epidemics in Israel, the virus has been isolated from the blood serum and passed to adult mice and hamsters by the intracerebral route, and to eggs by the yolk sac or onto the chorioallantoic membrane, leading to death of the embryo. The clinical features of the disease which mainly affected young adults were as follows [Goldblum *et al* (177)] There was a sudden onset with malaise, chilliness, fever, and drowsiness Severe frontal headache, aching of the eyes when moved, and pains in chest and lumbar region occurred. There was a rapid rise of fever to 38 to 39° C. Some patients developed nausea, anorexia, and

(169) reported 22 cases following the use of human thrombin prepared from Cohn's Fraction III and Hsia *et al.* (170) reported 4 cases among 16 children receiving Cohn's Fraction IV derived from pooled post partum plasma.

Size of virus.—McCallum (171) has presented evidence from human volunteer studies of gradocol membrane filtered material that the size of the SH virus is 26 mμ in diameter.

MISCELLANEOUS VIRUSES

In the period under review preliminary information has been reported on several new viruses.

New exanthematous disease.—Neva, Feemster & Gorbach (172) report the occurrence of an epidemic in Boston and vicinity in the late summer of 1951. This was characterized by varying degrees of fever which, in adults particularly, might be high and associated with chills and myalgia In over half the cases the fever preceded, and in most of the remainder was coincident with, the eruption of a maculopapular rash which varied from a few discrete pink lesions to a florid morbilliform rash. The rash was prominent on face and upper trunk as a rule, but frequently occurred over arms, buttocks, and legs. It lasted less than 48 hr. in the majority of cases, rarely less than 24 hr., and in one-third lasted over 48 hr. Mucous membrane lesions in the form of vesicles followed by punched out ulcers occurred, in about one-fourth of the cases, on the palate and tonsillar pillars, and rarely on other portions of the buccal mucous membrane. Lymphadenopathy was not a prominent feature of the illness. Since this epidemic did not appear identifiable with any of the recognized exanthemata it was considered to be a disease *sui generis*. From the stools and throats of patients suffering from the disease just described Neva & Enders (173) report the isolation of a cytopathogenic agent in tissue culture of various human tissues The agent appeared to cause destruction of the fibroblasts more readily than the epithelial cells The patients developed neutralizing antibodies against this agent and antibodies were also detected in others involved in the epidemic from whom no virus was isolated This virus is not related to the "orphan" viruses that have been isolated from patients diagnosed as having poliomyelitis or to other known viruses

Virus of roseola infantum.—Another agent was isolated by Neva & Enders (174)[2] from the feces of a two-year-old boy suffering from a disease that resembled roseola infantum during the epidemic just described. The boy had a temperature of 102 to 104° F for four days associated with a conjunctivitis, follicular tonsillitis, and lymphadenopathy. On the fourth day the temperature fell to 100° F and a maculopapular eruption which developed on his trunk lasted two to three days The agent was cytopathogenic for epithelial cells rather than fibroblasts, although both cell types were eventually involved

[2] Now identified as a Type 3 adenoid-pharyngeal conjunctival virus. [Huebner, R J., Rowe, W P, Ward, T G, Parrott, R. H, and Bell, J A, *New Engl J Med*, 251, 1077 (1954)].

in mild cases, up to 105° F. or over in severe cases. There is a marked polymorphonuclear leucocytosis in all but the mild cases, with a shift to the left and a decrease in platelets. (*b*) Hypotensive: About the fifth day of the disease hypotension or shock may occur. This is apparently due to loss of plasma through damaged capillary walls. Proteinuria develops rapidly and the specific gravity of the urine becomes fixed (*c*) Oliguric: With recovery from hypotension blood pressure may go above normal. Severe oliguria develops associated with a rising blood urea nitrogen, hyperkalemia, and hypocalcemia. Hemorrhagic phenomena such as ecchymoses, gastrointestinal hemorrhages, and hematuria develop about this time. At the end of this phase, about the ninth to tenth day in severely ill patients, pulmonary edema and central nervous system disturbances occur. (*d*) Diuretic: Clinical improvement tends to coincide with the onset of this phase. Proteinuria disappears and blood urea nitrogen returns to normal Diuresis may be so great as to lead to shock for a second time. Convalescence is apt to be prolonged after a severe attack associated with anemia and inability of the kidneys to concentrate. Mortality was 10 per cent among the Russian and Japanese cases and among the United Nations' soldiers also, until early evacuation of patients reduced it to 5 per cent among the latter group. In Korea the disease was geographically limited to above the thirty-eighth parallel, and epidemiologically was associated more with chiggers than any other arthropod [Gauld & Craig (185)]. There was a decreased incidence reported after instituting control measures that had been found valuable in the control of mite typhus.

Vigorous attempts have been made by the American workers to find the causative agent but none was isolated in a wide variety of laboratory animals or in tissue culture However, the Russian workers have reported the isolation of an agent by intravenous inoculation of human volunteers with the blood or urine taken from patients during the height of the fever. It was not transmissible by mouth or nose or swabbing on the tonsils. In the human host it had been passed in series through four "generations." The incubation period was 12 to 24 days and one attack conferred immunity. Convalescent human serum could stop the development of the disease. The agent was filterable through a size V Berkfeld filter [Mayer (181)]

Pregnancy and Virus Infection

Rubella.—The relation of rubella in first trimester of pregnancy and congenital defects is now widely recognized and information up to 1951 was reviewed by Burnet (2). The difficulty of estimating the risk of damage was mentioned since all the studies up to then reported were retrospective and indicated a risk of about 80 to 90 per cent Since that time a few prospective studies have been reported Ingalls & Purshottam (186) in a study of 72 cases found the incidence of fetal abnormalities to be 17 per cent; Lundström (187) studied 1067 pregnant women with rubella during an epidemic in Sweden and found the incidence of neonatal death and congenital abnormalities to be 17 per cent as opposed to 6 per cent in uninfected women; and

dryness of the throat. On physical examination the face was characteristically flushed; the throat was red in a few patients, but signs of upper respiratory infection were characteristically absent. A general lymphadenopathy was common and the spleen might be enlarged. The nodes were firm and tender. In a very few patients transitory meningeal involvement occurred, with pleocytosis and increased protein in the spinal fluid. In many patients a maculopapular rash occurred mostly over the trunk. A leucopenia with a relative lymphocytosis was characteristic. The temperature remained high for two to three days falling by lysis The illness was self limited to three to six days, but relapses were common and convalescence was slow. No sequelae had been noted. The patients developed complement fixing antibodies The vector was considered to be either *Culex molestus* [Bernkopf (178)] or *Aedes aegypti* [Davies & Yoshpe (179)]. The incubation period was two to six days.

Measles—Enders & Peebles (180) report the isolation of several strains of a cytopathogenic agent from both the blood and throat washings of patients with measles in tissue cultures of either human or simian renal cells. Microscopic examination of the infected tissue culture revealed the formation of syncytial giant cells containing 40 to 100 nuclei. The nuclei showed typical acidophilic intranuclear inclusion bodies surrounded by a clear halo. A complement-fixing antigen developed in the fluid phase of the tissue cultures which reacted with the serum of patients recovered from measles but not with that of patients early in their disease The sera of two patients convalescent from measles were shown to develop a neutralizing capacity for the cytopathogenic effect of a strain of virus isolated from a third patient. Such a neutralizing effect was not observed in the sera taken early in their disease. The final proof of the specificity of this culture virus by its transmission to humans and monkeys and its recovery from those hosts remains to be done.

Epidemic hemorrhagic fever.—The recognition of this disease was recorded in Volume 5 (1954) of the *Annual Review of Medicine* [Jawetz (3)]. The work done on this disease by the Russian and Japanese workers before World War II indicates that it is due to an arthropod borne virus [review by Mayer (181)] It appears as if this were but one of several types of hemorrhagic fever that occur in Russia which are transmitted by arthropods [Gajdusek (182)]. Further information has now become available from the American work in Korea Barbero *et al.* (183) in 1952 described a study of 31 patients with this disease. Moreover, an extensive symposium, reviewing studies conducted during the care of 613 patients, has just been published by Earle (184). This is an acute disease characterized by a variety of physiologic disturbances which tend to fall into four phases (*a*) Febrile: This usually has an abrupt onset with chills followed within a few hours by prostration, thirst, and anorexia. Headache, diffuse aching, and sometimes acute abdominal pain, occur early. There is an erythematous flush of face and upper trunk and petechiae are present, usually in the axillary folds The height of the fever depends on the severity of the disease, ranging from 100 to 103° F.

in mild cases, up to 105° F. or over in severe cases. There is a marked polymorphonuclear leucocytosis in all but the mild cases, with a shift to the left and a decrease in platelets. (*b*) Hypotensive: About the fifth day of the disease hypotension or shock may occur. This is apparently due to loss of plasma through damaged capillary walls. Proteinuria develops rapidly and the specific gravity of the urine becomes fixed. (*c*) Oliguric: With recovery from hypotension blood pressure may go above normal. Severe oliguria develops associated with a rising blood urea nitrogen, hyperkalemia, and hypocalcemia. Hemorrhagic phenomena such as ecchymoses, gastrointestinal hemorrhages, and hematuria develop about this time. At the end of this phase, about the ninth to tenth day in severely ill patients, pulmonary edema and central nervous system disturbances occur. (*d*) Diuretic: Clinical improvement tends to coincide with the onset of this phase. Proteinuria disappears and blood urea nitrogen returns to normal. Diuresis may be so great as to lead to shock for a second time. Convalescence is apt to be prolonged after a severe attack associated with anemia and inability of the kidneys to concentrate. Mortality was 10 per cent among the Russian and Japanese cases and among the United Nations' soldiers also, until early evacuation of patients reduced it to 5 per cent among the latter group. In Korea the disease was geographically limited to above the thirty-eighth parallel, and epidemiologically was associated more with chiggers than any other arthropod [Gauld & Craig (185)]. There was a decreased incidence reported after instituting control measures that had been found valuable in the control of mite typhus.

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Greenberg (188) in New York City studied a group of 83 pregnant women with rubella and also found the risk of fetal loss (11 per cent still birth) or damage to be 17 per cent. Krugman & Ward (189) summarized the problem and emphasized the importance of weighing the risks when a pregnant woman contracts rubella, and individualizing recommendations for abortion on the basis of such things as the age of the parents and the social and religious background. The value of gamma globulin as a prophylaxis in this disease is very uncertain. Korns (190) found a statistically significant protection with one lot of gamma globulin in one controlled test but not in three others similarly conducted with other lots of gamma globulin. Laudon *et al.* (191) reported definite protection in an institution of 133 children, and that the cases among the gamma globulin group were one-third of those among the controls (6:18). Anderson & McLorinan (192) were not able to achieve a statistically significant protection during an epidemic among a group of 45 boys by means of 4 ml. of rubella convalescent gamma globulin The decision to use gamma globulin in a woman exposed to rubella should take this uncertainty into account and also the fact that fetal damage may occur from a modified infection. Gamma globulin may modify the disease and thus mask the true diagnosis. The danger of a modified infection can be compared with the earlier demonstration by Krugman *et al.* (193) that the blood of a patient suffering from rubella without a rash was infectious for volunteers.

Other Viruses

The damaging effect of rubella on the fetus has naturally turned the attention of the profession to the effect of other viruses There appears to be relatively little information available The situation up to 1951 was summarized by Swan (194) He pointed out that small pox, pandemic influenza, and measles to a lesser extent, led to a termination of gestation, but that vaccination seemed to have no effect on the fetus.

Vaccination.—MacArthur (195) surveyed by questionnaire 5000 women, of whom 203 were pregnant when successfully vaccinated because of an epidemic of small pox. Among the 33 vaccinated in the first month there was one miscarriage, among the 34 vaccinated between the fourth to twelfth week there were ten miscarriages, five stillborn, and one congenital anomaly. If the first trimester is included as a whole, fetal loss consisted of 24 per cent, whereas among those vaccinated in the second and third trimester, fetal losses were 3 and 2 per cent respectively. This loss is significantly greater than the highest expected normal loss of 13 per cent [Randall *et al* (196)]. This evidence would suggest that vaccination during the first trimester must be taken as a calculated risk

Mumps.—Bowers (197) has reviewed 84 reported cases of mumps in pregnant women In nine of these, the fetus died and in twelve the infant was deformed.

Influenza.—Campbell (198) studied two groups of women, 164 who had influenza A prime type during the early months of pregnancy and 825 who had escaped. He could find no difference between the groups.

Measles —Christensen *et al.* (199, 200, 201) had the opportunity of seeing an epidemic of measles among a population in South Greenland. The morbidity rate was 999 per 1000; the mortality rate was 18 per 1000. About half of the pregnant women aborted, but no congenital abnormalities were noted among the living infants born of mothers who had measles during their pregnancy.

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DISEASES OF THE GASTROINTESTINAL TRACT[1] (LIVER)

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There will be no attempt in this review to cover the many advances in gastro-enterology which have been made during the past year, not only because the authors are not fitted to judge the merits of the many papers that have been published, but also because such an excursion has a tendency to lead to a review as dry and tedious as the genealogy of David in the First Book of Chronicles. In an attempt to avoid this hazard, the bulk of this review will deal with recent papers and current concepts in liver diseases, and relatively little space will be devoted to papers more directly concerned with the gastrointestinal tract A series of articles on various aspects of liver disease that deserve special mention have appeared during 1954 in the *American Journal of Medicine* under the title of "Seminars on LiverDisease." These articles written by experts in the field are worth detailed study. It will be convenient to follow the pattern set by previous reviewers and discuss the papers in a regional fashion.

Cirrhosis of the Liver

Esophageal varices—Although the presence of portal hypertension can usually be strongly suspected on clinical grounds, the recognition of dilated veins in the lower two-thirds of the esophagus provides useful, confirmatory evidence that the pressure within the portal circuit is elevated. Large esophageal varices, however, are not necessarily pathognomonic of cirrhosis of the liver, since other conditions giving rise to an elevation of pressure within the portal system may result in their development (1, 2, 3). Spontaneous fluctuation in the size of esophageal varices has been recently emphasized by Bennett *et al.* (4), who reported that occasionally patients in whom varices had been clearly demonstrated radiographically were found, at operation, to have a normal portal pressure. This finding underscores afresh the old observation that small spontaneous changes in the portal pressure may occur in some patients with cirrhosis of the liver.

The ideal method for the demonstration of esophageal varices continues to be a subject of animated discussion. Brick & Palmer (5) have recently reported interesting findings based on a study of 150 cases of cirrhosis of the liver Of all patients examined 63 3 per cent were found to have esophageal varices which were visible on direct esophagoscopy, whereas only 21 per cent of these cases had varices that were demonstrated on radiographic examination. Thus the authors feel that esophagoscopy should be preferentially undertaken whenever varices are suspected. This enthusiasm for

[1] The survey of literature pertaining to this review was completed in August, 1954.

esophagoscopy, however, is not entirely shared by other workers who feel that, with special techniques (6, 7), the majority of esophageal varices can be adequately visualized radiographically. The recent demonstration by Palmer (8) that the performance of the Valsalva maneuver will increase the pressure within the esophageal varices suggests that it may be used as an aid to their radiological demonstration. Although the danger of rupture of esophageal varices appears to be slight during esophagoscopy (9), the necessity for an expert endoscopist and the discomfort to the patient have restricted routine esophagoscopy in patients with cirrhosis of the liver to a few active research centers. The frequency of gastric varices in patients with portal hypertension has been recently emphasized by Evans *et al.* (10) who, by using careful radiological technique, were able to demonstrate gastric varices in 24 out of 40 cases of portal hypertension.

An investigation into the primary pathological processes which lead to rupture of the varices has been made by workers at the Mayo Clinic (11). A pathologic study was made of 91 cases of bleeding esophageal varices, and in 56 per cent ulceration of the esophagus was sufficiently severe to suggest to these authors that rupture of the varix was precipitated by the ulcerative process. In only 39 per cent was no esophageal ulceration found and the rupture of the varix ascribed to the hydrostatic pressure alone. It is suggested by these authors that the presence of esophageal varices impairs the nutrition of the surface epithelium of the esophagus which becomes more susceptible to ulceration by the regurgitation of acid gastric juice.

The over-all mortality figures for bleeding esophageal varices continues to be distressingly high The prompt and skilled use of the Sengstaken-Blakemore esophageal tube in association with replacement transfusion remains the procedure of choice in the emergency treatment of esophageal varices Use of this tube has reduced the mortality from about 80 per cent to 50 per cent or less, depending upon the skill and experience of the operator (12) A recent article by Blakemore (13) has also emphasized that, if good results are to be obtained, the balloon should be kept at a pressure that prevents bleeding for at least 72 hr and should remain in position for 24 hr. after the balloon is deflated That constant vigilance is required as long as the balloon is in place cannot be overstressed. In some cases of esophageal hemorrhage an emergency transesophageal suturing of the ruptured varices has been recommended (14) Other emergency operations which have been advocated include subcardiac porta-azygos disconnection (15) and a combined ligation of the hepatic and splenic arteries (16) When the varices are the result of extrahepatic portal obstruction transesophageal obliteration of the varices has been advocated by Crile (17) None of these operative procedures, however, appear entirely satisfactory If bleeding continues unchecked, coma will rapidly supervene in the majority of cases of cirrhosis of the liver, and the operative mortality will become prohibitively high. In rare cases recurrence of esophageal bleeding follows the gradual release of the pressure within the esophageal balloon. Provided the patient

can withstand a surgical operation, an emergency portacaval shunt, performed with a balloon still in place, is probably the treatment of choice.

Portal pressure.—In recent years increasing attention has been paid to the consideration and estimation of the degree of portal hypertension in patients suffering from cirrhosis of the liver As a result of the work of Volwiler and others (18, 19), it has become abundantly clear that, although elevation of the portal pressure alone will not cause ascites, the localization of fluid within the peritoneal cavity is directly related to the height of the portal pressure.

The estimation of the portal pressure without recourse to surgery has been attempted in many ways and is evidence of the increased realization that a reliable estimation of the portal pressure would be of prime importance in the understanding of the problems of hepatic cirrhosis and ascites The inacessability of the portal vein is the chief obstacle to the measurement of the portal pressure in intact man, and the various methods which have been devised to overcome this difficulty testify to the ingenuity and persistence of the clinical investigator. An early attempt to measure the portal pressure in intact man was made by Bean and co-workers (20). These workers observed blanching of the mucosal surfaces of the lower bowel, by means of a sigmoidoscope or proctoscope, when the intraluminal pressure was raised. Technical difficulties and the uncertainty of the anatomical communications of the mucosal vessels have tended to diminish the popularity of this method in recent years Davidson and his colleagues (21) have reported the direct measurement of the pressure in a collateral abdominal vein. The abdominal vein is obstructed by digital pressure above the point at which the pressure is recorded This method, despite its relative simplicity, is not used more widely because of the uncertainty of the anatomical connections of the abdominal collateral veins.

Another method of some interest which has recently been developed for measuring portal pressure is the so-called hepatic occlusion method (22, 23, 24) It is the contention of these groups of workers that occluded hepatic vein pressure measures hepatic intrasinusoidal pressure which in turn reflects the portal venous pressure There is evidence from work done on animals in support of this concept since hepatic occlusive pressure and portal vein pressure measured simultaneously at operation are identical (25) However, the circulatory dynamics of the human liver are complicated considerably by its dual blood supply, and there are theoretical objections to the belief that hepatic occlusive pressure measures true portal pressure. It is of particular interest, therefore, that such a good correlation between hepatic occlusive pressure and the pressure in the portal vein found at operation was observed by Sherlock and co-workers (23) Despite the undoubted pragmatic advantages of this method of estimating portal pressure, it carries the distinct disadvantage of requiring all the facilities necessary for hepatic vein catherization To overcome the complexities inherent in this method the above authors have also used the method of percutaneous

splenic puncture (26). In this method, a fine lumbar puncture needle 7 cm. long is inserted between the eighth and ninth intercostal spaces and directed in a cephalad direction at an angle of 45° to the transverse plane. The needle tip lies in the splenic pulp which is connected by means of polyethylene tubing to a strain gauge and the intrasplenic pressure recorded thereon. Pressures recorded in various parts of the spleen did not differ by more than 3 mm of mercury. In 14 patients without portal hypertension the intrasplenic pressure was found to be 3 to 17 mm. of mercury. In 11 patients with portal hypertension attributable to cirrhosis of the liver the recorded pressure was 25.5 mm. of mercury. An extremely good correlation between occluded hepatic vein pressure and splenic pressure was found. A fall in intrasplenic pressure of 17 mm. of mercury was observed after a portacaval anastomosis had been carried out on one patient (26). Fear that serious intra-abdominal hemorrhage might follow this procedure has so far been groundless but the authors point out the necessity of using a fine needle and prohibiting deep respiration by the patient during the procedure As might be anticipated the intrasplenic pressures recorded in patients with tense ascites were falsely high. This method of estimating portal pressure has the virtue of simplicity and, if the safety of the procedure can be confirmed in a large series of cases, it would seem likely to be used more extensively in the future

Yet another method of estimating portal pressure is based on a knowledge of the physiological balance which normally exists between the serum and tissue hydrostatic and osmotic forces According to these principles first enunciated by Starling in 1896 (27), the portal pressure minus the ascitic hydrostatic pressure should equal the difference in osmotic pressure between the serum and ascitic fluid. This difference has been recently used by Giges & Kunkel (28) to estimate the effective portal pressure in patients with cirrhosis of the liver and ascites Although these workers found a poor correlation between the serum osmotic pressure and the presence of ascites, the osmotic difference between the serum and ascitic fluid reflected to some extent the effective portal pressure However, important limitations of the osmotic pressure method for determination of effective portal pressure became apparent during the study. When the serum osmotic pressure was very low, the ascitic fluid osmotic pressure was similarly lowered, and when the ascitic fluid osmotic pressure was less than 15 mm. of mercury, the osmotic difference no [illegible]

ascitic fluid occurs by way of the lymphatic system (29) This method of estimating the effective portal pressure would doubtless be more popular if os- [illegible]

ducing considerable error

A direct approach to the portal vein in intact man has been made by

Bierman and co-workers (31) who inserted a long needle directly through the liver substance into a tributary of the portal vein. The needle can be connected to a recording manometer and the portal pressure recorded directly. Although this procedure is reported to be safe, the technical difficulty of entering a portal tributary and the potential dangers of the method have so far precluded its general adoption. Direct measurement of the venous pressure within the esophageal varices through an esophagoscope has also been used by some workers (32, 33) as an index of portal hypertension but has found little general favor.

In reviewing the many methods that are being currently employed for the estimation of portal pressure, one is struck by the limitations of the methods so far devised. Many procedures yield approximations but few, if any, can combine simplicity and elegance with trustworthy accuracy and, despite the notable advances already made, one would welcome the arrival of physiologists, accustomed to dealing with the complex problems of hemodynamics, into this difficult and controversial field.

Splenic portal venography.—The differentiation between intrahepatic and extrahepatic obstruction of the portal vein can usually be made clinically. Although extrahepatic obstruction may be suspected, the site and extent of the obstruction may be obscure. The value of the classic pioneering work of Moore (34), Child (35), and others, utilizing the injection of radio-opaque material into the spleen or portal vein to delineate the obstruction during laparotomy, cannot be underestimated However, the recent introduction of splenic portal venography (26, 36 to 40) enables visualization of the portal system to be undertaken prior to operation. The technique adopted by most workers differs only in detail. After preliminary infiltrative local anesthesia, 20 cc. of 70 per cent of diodone are rapidly injected into the spleen through an 18 gauge needle. The procedure is usually unaccompanied by pain though some patients experience transient nausea. Hemorrhage of the spleen has not proved a danger provided a needle not larger than a size 18 is used Walker (41) has reported an isolated case of hemorrhage which followed the use of an unnecessarily large needle. Although the leakage of diodone into the peritoneal cavity may rarely occur, it does not usually cause recognizable ill effects. Indeed, 20 cc. of 70 per cent diodone has been inadvertently injected directly into peritoneal cavity without ill effects(38). Following injection of the radio-opaque material, the dye rapidly leaves the spleen and the sizes of the splenic and portal veins are revealed In patients in whom the portal pressure is not raised a small filling defect where the superior mesenteric vein joins the splenic vein is a usual finding In severe intrahepatic obstruction attributable to cirrhosis of the liver some reflux of the dye along the superior mesenteric vein may occur and collateral vessels are well visualized and indicate some reversal of flow. The portal vein may appear grossly dilated. When local extrahepatic portal obstruction is present the radiographic appearances are usually distinctive. Cavernomatous transformation is suggested by a mottled irregular appearance of the splenic or

portal vein and by delayed filling of the intrahepatic branches. Although the suspected presence of portal hypertension is the main indication for percutaneous venography, it also provides a useful method of determining the patency of a portacaval anastomosis (42). Usually, however, the patency of a portacaval shunt is obvious clinically or can be determined by less elaborate methods (43). The determination of the portal circulation time is a simple method which is commonly employed When ether vapor is rapidly injected into the rectum a variable period of time elapses before its presence can be detected by the patient Following the successful completion of a portacaval shunt a diminution in the portal circulation time is a finding which is sufficiently constant to be used as evidence that the shunt is patent (44).

Surgical relief of portal hypertension.—The surgical hurly-burly which followed the realization that relief of portal hypertension could be accomplished by operative means has not yet subsided, and the place of surgery in the management of patients with cirrhosis of the liver still remains to be determined. However, as surgical experience increases and the operative mortality falls the indications for surgical intervention are increasing. The report of Patek and coworkers in 1948 (45) that 50 per cent of patients who had an esophageal hemorrhage died within one year after the first bleeding provided a considerable impetus to surgical endeavor, and hemorrhage from esophageal varices undoubtedly still remains the single most important indication for surgical intervention. Unfortunately, even prompt emergency treatment for the initial hemorrhage from esophageal varices carries a significant mortality. In one series of 66 cases of cirrhosis of the liver reported by Merendino & Volwiler (46), 17 per cent of patients died of the first hemorrhage from esophageal varices In country districts where adequate medical treatment may be delayed the mortality is unquestionably higher. These considerations have led some workers (47) to advocate portal decompression in patients with mild cirrhosis of the liver who have not yet bled from demonstrable esophageal varices

Although operative treatment should preferably be carried out on patients with minimal disturbances of hepatic function and without ascites, a recent trend towards relaxing the rigid criteria of yesteryear is becoming evident and complicating ascites is no longer a necessary contraindication to surgical operation (48 to 51) The decision to operate will depend upon a variety of factors If, in addition to ascites, the patient is deeply jaundiced and has a greatly reduced serum albumin level, operation is extremely hazardous. The presence of severe jaundice appears to be a greater contraindication to operation than the level of serum albumin If jaundice is minimal and the bilirubin is below 5 mg per cent and the serum albumin not greatly decreased, surgical intervention appears justifiable (51) The dangers of such an operation should, however, not be considered lightly and careful selection of patients is required if satisfactory results are to be obtained. The final decision to operate should depend as much upon a careful clinical appraisal

of the patient as upon any one chemical abnormality. Apart from the immediate postoperative mortality disquieting symptoms may arise during convalescence and recovery. A sharp increase in the serum bilirubin which is unaccompanied by any deterioration in other liver function tests may occur early in the postoperative period. In some patients this elevation of bilirubin persists during convalescence and may become permanent. Dependent edema of the legs which at times is severe and incapacitating has been a feature of some cases This edema is probably more closely related to the level of the serum albumin than to any increase in the inferior vena caval pressure. However, since the operation in these patients is frequently life saving, and the protuberant dropsical belly frequently disappears, moderate edema of the legs is of relatively little import. Another complication of a portacaval shunt in patients with severe cirrhosis of the liver has recently come to light (51). A few patients may for the first time experience the gradual onset of drowsiness which may progress to deep stupor On other occasions disorientation and inappropriate behavior are predominant. The duration of these symptoms is variable but rarely lasts more than a week Recovery may be as abrupt as the onset and usually occurs within 48 hr These symptoms are not classical of hepatic coma and usually occur when the patient has already weathered the storm of the immediate postoperative period. The cause of these untoward symptoms is somewhat obscure and, although it is tempting to ascribe them, at least in part, to ammonia intoxication, such an explanation is probably unjustifiably naive Chlortetracycline (aureomycin) has appeared to terminate the episode prematurely in some cases but, since recovery is usually spontaneous, the evaluation of the possible usefulness of this drug is extremely difficult.

Therapy of ascites—The most significant development in the treatment of the massive abdominal fluid found in the great majority of patients with severe cirrhosis continues to be the use of low sodium diets (52, 53, 54). Restriction of dietary sodium to approximately 17 m eq per day has proven of definite value in preventing the further accumulation of ascitic fluid. The fluid is not eliminated but the amount that is formed can be well-controlled, thus preventing frequent paracenteses and the resulting drain of body protein and other nutrients The profound vascular alterations of paracenteses themselves have also received recent emphasis (53). The ability of patients with cirrhosis to tolerate extreme sodium restriction for long periods of time without ill effects has now been demonstrated The classical "low salt syndrome" is rarely encountered In the series of cases studied by Eisenmenger and associates (52) two patients out of a group of 25 developed evidence of toxic symptoms which were readily reversed by a return to a higher sodium intake Associated renal disease appears to augment these toxic symptoms.

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the eventual general improvement of these patients. Diets containing as much as 150 gm. of protein per day have been tolerated by many of these patients for prolonged periods.

There is little evidence that the sodium restriction per se is beneficial to the cirrhotic liver. The eventual improvement of certain of these patients is primarily the result of a good diet. Early beneficial effects can be most readily detected by the appearance of an increased sodium excretion in the urine (52). The use of mercurial diuretics may be of some benefit, particularly in those patients who are excreting significant amounts of sodium. Ammonium chloride, although it has been shown to produce symptoms of hepatic coma sometimes (55), does not appear to be contraindicated when used with caution.

The new diuretic, acetazoleamide (Diamox: 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide), has attracted considerable attention recently and has been tested in patients with cirrhosis by a number of workers (56, 57). Thus far only limited success has been achieved. The patients with a strong tendency to form ascites and very little sodium in the urine are usually refractory to Diamox. Toxic symptoms of drowsiness and irrational behavior have been noted in some of these individuals (57). Certain patients with a somewhat lesser tendency to form ascites may be benefited by Diamox. In the authors' experience, patients who have shown some response to dietary therapy or whose portal pressure has been reduced by means of a portacaval shunt have been benefited to some degree by this further therapeutic supplement.

In some instances albumin injections also produce an increase in urinary sodium and a decrease in ascites (19) and here again this occurs primarily in patients with relatively low portal pressure and only a moderate tendency to form ascitic fluid. This is particularly true for certain young individuals in whom very low serum albumin levels appear to play a more dominant rôle in the mechanism of the ascites Albumin injections are of little benefit in the ordinary patient with very low levels of sodium in the urine and a great tendency to form ascites.

Despite considerable progress in the dietary therapy of patients with cirrhosis and ascites, a significant percentage of patients are still encountered who remain refractory to treatment and continue to form ascites despite long periods of adequate food intake while on a low sodium diet. Surgical relief of the portal hypertension by means of a portacaval anastomosis should be strongly considered in these individuals. Although certain early observations (48, 57) suggested a beneficial effect of this operation on ascites, most surgeons have reserved this operation for patients suffering from esophageal hemorrhages Recently Eisenmenger & Nickel (51) have reinvestigated this problem and found definite indications of relief of ascites in certain individuals Their experience indicates, however, that many factors must be considered in each individual patient The most common complication encountered has been episodes of mental stupor similar to those described by McDermott & Adams (58)

Hepatic coma.—Hepatic coma has been produced experimentally in dogs by graded ischemia of the liver (59 to 62). The operation, as performed by Rappaport (61), is usually carried out in two stages The first stage is performed by the ligation of the portal vein in the hepatoduodenal ligament and the construction of a portacaval anastomosis. The second stage carried out 24 to 48 hr. later consists of ligation of the hepatic artery. Careful postoperative care, including the administration of antibiotics and intravenous glucose, is needed if the animals are to survive. Widespread centrilobular necrosis is a characteristic finding in those dogs who survive the operation Following the operations the dogs exhibit symptoms and signs similar to those found in cases of typical hepatic coma in humans: restlessness, anorexia, vomiting, and jaundice are common Deep coma with muscular rigidity and occasional twitchings are also observed Abnormal electroencephalograms have been recorded (61) Hepatic fetor, though not found in dogs with classical coma, was occasionally observed in animals with chronic ischemia of the liver.

The nature of the elusive substance responsible for the characteristic hepatic fetor has been investigated by workers in the Mayo Clinic for many years, and although the precise nature of the material has not yet been determined, some extremely interesting observations have been made (63). In several instances hepatic fetor has been noted in patients in whom liver injury could not be detected. The characteristic odor has been noted in the urine of control subjects as well as in the urine obtained from patients with liver disease. It has also been observed that the fetor may disappear after a large bowel movement or after the administration of an enema (64). Sterilization of the bile by administration of antibiotics, however, does not alter the degree of hepatic fetor. The most recent evidence suggests that the fetor may be attributable to a tertiary amine having five or more carbon atoms (63).

Ammonia metabolism and hepatic coma—Although much has been learned about hepatic coma since it was first clearly recognized in the middle of the last century, the precise pathogenesis of the condition remains as obscure as ever. The reason for the well-known observations that a small hemorrhage or an infection will precipitate an episode of coma in a previously compensated cirrhotic, is also incompletely understood

Kirk in 1936 (65) was the first person to investigate ammonia metabolism in liver disease in a systematic fashion He found an increased blood ammonia level in 82 per cent of patients suffering from cirrhosis of the liver and concluded that the rise in blood ammonia was a result of the presence of the portal collateral circulation which permitted portal venous blood containing a high ammonia content to reach the peripheral circulation without first passing through the liver Renewal of interest in ammonia metabolism in liver disease has stemmed from a number of recent observations The use of cation exchange resins in the control of various edematous states has lead to its trial in patients with cirrhosis of the liver and ascites (66). Although in some cases a diminution in the formation of ascites followed the administration of resins, disturbing toxic symptoms were soon observed In an early report by

Gabuzda *et al.* (67) 6 out of 8 cases of cirrhosis of the liver who received ammonia resins developed drowsiness, apathy, confusion, and a coarse flapping tremor. The clinical condition engendered by the administration of these resins was indistinguishable from spontaneous hepatic coma occurring in patients with cirrhosis. Since this syndrome did not occur in patients given potassium or hydrogen resins, it seemed possible that the symptoms were related to the ammonia moiety of the resins. Further work (55, 68) confirmed the toxicity of the ammonia resins when given to patients with cirrhosis of the liver, and it was suggested that the toxic symptoms might be related to an elevated blood ammonia. The correlation, however, was insufficient for these authors to consider that a causal relationship had been firmly established between an elevated blood ammonia and the neurological symptoms

McDermott (58) has recently reported an instance where during the course of pancreaticoduodenectomy in a patient suffering from a carcinoma of the pancreas it became necessary to resect the portal vein and to join the superior mesenteric vein to the side of the inferior vena cava. An Eck fistula in a patient with a normal hepatic function was thus performed. Postoperatively this patient developed attacks of confusion, stupor, and occasional episodes of coma. These attacks were transitory in nature and left no neurological sequelae Electroencephalograms taken during the heights of the coma were found to be identical with those recorded in patients exhibiting typical hepatic coma It was observed that these attacks which occurred spontaneously could also be induced by the ingestion of ammonia ion exchange resins, ammonium chloride, or a diet containing a high protein content. Although the onset of the symptoms was correlated with a sharp rise in the levels of ammonia in the peripheral blood, the mental disturbances of the patient persisted after the ammonia levels had returned to normal. The good correlation between the mental disturbances and the blood ammonia in this case is in contrast to the finding reported above.

Traeger and co-workers (68) have utilized ammonia tolerance tests to investigate the ammonia metabolism in patients with cirrhosis of the liver. Patients with cirrhosis without neurological complications exhibited blood ammonia levels that were distinctly higher than those found in normal controls Moreover, the rise in blood ammonia following the ingestion of a standard dose of ammonium chloride was greater in patients with cirrhosis of the liver than in normal subjects A study of ammonia metabolism in patients with cirrhosis of the liver has also been made by Riddell & McDermott (69). Although a high blood ammonia was reported both in patients with mild cirrhosis and in patients in a precomatose condition, a fall in blood ammonia was not regularly associated with clinical improvement nor with diminution in the depth of the comatose condition.

Recently Walshe has fully summarized the disturbances in amino acid metabolism in two excellent reviews (70, 71) Glutamine was found to be the chief ninhydrin positive substance in the spinal fluid of patients suffering from hepatic coma. In addition, a reversal of the normal plasma alanine

glutamine ratio was observed Plasma glutamine has been determined in normal subjects and patients with cirrhosis of the liver by the use of the specific glutaminase obtained from *Clostridium welchii* by Seegmiller and coworkers (72). The plasma glutamine concentration was found to be the same in both groups. Moreover, no correlation between the plasma glutamine level and the neurological state of the patients could be elicited. Increasing the blood ammonia concentration by an intravenous infusion of ammonium chloride likewise did not alter the plasma glutamine concentration. It is relevant in this connection to note that, although an increased glutamine content of the brain, muscle, and plasma is commonly found in hepatectomized dogs, the plasma glutamine does not reflect the concentration of glutamine in the brain (73). An increase in the glutamic acid content of the cerebrospinal fluid in some patients with cirrhosis of the liver has been reported by Walshe (70), who has also postulated that hepatic coma may be related to a failure of the normal, ammonia binding mechanism of the brain and, as a consequence, glutamic acid can no longer combine with ammonia to form glutamine. In a preliminary communication, Walshe (74) reported encouraging results in the use of glutamic acid administered to patients with cirrhosis of the liver with hepatic coma. Five episodes of coma occurring in three patients with cirrhosis of the liver were each treated with 23 grams of sodium glutamate On each occasion a return of consciousness followed the administration of the drug Riddell & McDermott (69) treated 11 cases of hepatic coma with sodium glutamate, six of whom improved while on therapy A good response has also been reported by other workers (75) Singh, Barclay & Cooke (76), however, administered sodium glutamate to four patients with hepatic coma without noticeable improvement Other workers, including the present authors, have also failed to observe improvement in hepatic coma following the administration of glutamic acid (77, 78) Rappaport *et al* (61) infused glutamic acid into the carotid arteries of two dogs in whom liver insufficiency had been produced experimentally, and, although the glutamic acid in the cerebral circulatory bed was raised 20 times the normal value, the animals showed no clinical improvement It must be concluded from a survey of recent literature that ideal treatment for hepatic coma is an extremely controversial subject, and it is hazardous at this juncture to bedeck glutamic acid with the capricious garland of therapeutic success

The neurological aspects of hepatic coma have been greatly clarified as a result of the work of Adams and co-workers (79, 80, 81). The most characteristic early symptoms of impending coma found by these workers were confusion and an insidious reduction of awareness As coma supervened, confusion progressed to extreme drowsiness, stupor, and eventual unconsciousness Concomitant with the change in the level of consciousness, striking spontaneous involuntary movements of the outstretched arms were commonly observed, and usually consisted of rapid, irregular, alternate, lateral deviations of the fingers and flexion-extension movements of the fingers and wrists. Electromyographic analysis revealed a consistent pattern of abnormality.

Rigidity of the limbs and dysarthria were frequent findings in cases of extreme severity. Extensor plantar responses were often found when deep coma was present. Patients in hepatic coma were found to have a consistently abnormal electroencephalogram which was characterized by paroxysms of bilateral, slow, synchronous, delta waves superimposed on a background of relatively normal alpha activity. Diffuse hyperplasia of protoplasmic astrocytes with little change in parenchymal structures were found to be the usual neuropathological findings. These changes have also been noted by Stadler (82) and Cammermeyer (83). In direct contrast to these findings severe parenchymal changes without astrocytic proliferation have been a feature of the cirrhotic patients studied by Baker (84). It is possible that the discrepancy in the findings of these two groups may be attributable to the fallibility of comparing groups of cirrhotic patients without due regard to their etiological basis.

Neurological manifestations of a dramatic and bizarre nature may occur in patients with Wilson's disease. Transient hemiparesis and nystagmus are not uncommon. Confusion, disorientation, and hallucinations may usher in frank convulsions and coma. The development of these symptoms is not correlated with hepatic decompensation and has been seen in patients with negligible hepatic dysfunction. Recovery with no neurological sequelae is the rule, although relapses are common Periods of unconsciousness for some weeks are not incompatible with complete recovery from the comatose condition (85).

Acute Viral Hepatitis

Length of Bed Rest.—The critical assessment of tried and honored remedies is one of the hallmarks of the modern approach to practical therapeutics It has always been an accepted tenet of treatment that patients with viral hepatitis should be confined to bed for a considerable period of time. The observation of Bradley (86) that the adoption of the upright posture results in a diminution of blood flow through the liver is often quoted (7) as evidence in favor of the desirability of such a regimen. However, a recent investigation carried out on United States troops in Germany and Korea has resulted in doubt of the importance of bed rest in the treatment of acute hepatitis (87). The advice issued by the Committee on Hepatitis of the Commission of Liver Diseases of the Armed Forces Epidemiological Board (88) is that patients suffering from acute viral hepatitis should be confined to bed only in the early acute stages of the disease and that, regardless of the degree of jaundice, as soon as the patient begins to feel well, confinement to bed is no longer indicated When the serum bilirubin has remained 1 5 mg. per cent or lower for one week and bromsulfalein retention less than 6 per cent at 45 min for a similar period of time, it is further recommended that the patients

point of view should probably be modified in elderly persons and in civilians in whom rapid convalescence is not so essential. The frequent occurrence of relapses during convalescence, particularly after unusual exertion (89) with ensuing prolonged periods of re-elevation of the bromsulfalein test (90), should instill an attitude of caution in the therapy of this condition which is known occasionally to develop into a chronic stage Prolonged convalescence is, however, undesirable once the patient is clinically and biochemically improved. Failure to return to work may precipitate an all too common iatrogenic posthepatitis syndrome

Diet.—A recent investigation has also been carried out on United States Army troops to assess the importance of a nutritious diet in the therapy of acute viral hepatitis. The mean duration of the acute illness was used as one of the criteria in assessing the efficiency of any particular dietary regimen. The shortest duration of the acute illness was noted in those patients who were placed on a high protein diet in which the protein accounted for 19 per cent of the total calories No increased benefit was obtained in those patients placed on a diet of 4000 calories per day compared with those on 3000 per day (91) It was of interest that incidence of early relapses appeared to be the same in both groups studied. These findings are in contrast to those of Leone *et al* (92) who found that patients placed on a high protein, high carbohydrate, low fat diet containing 200 gm of protein, 75 gm of fat, and 600 gm. of carbohydrate were benefited less than those placed on an ad libitum diet Although certain dangers of an excessively high protein intake in patients severely ill with hepatitis and in a precomatose condition have been emphasized by Phillips and co-workers (55), such a diet is not contraindicated in the usual case of hepatitis and cirrhosis That recovery from an acute attack of hepatitis can occur despite severe undernutrition and hypoproteinemia is illustrated by the recent report of Dible and co-workers (93).

Drugs.—The use of drugs such as chlortetracycline, ACTH, and cortisone should be considered only when patients with hepatitis fail to make the usual expected rapid recovery Chlortetracycline in a dose of 200 to 500 mg. four times daily has been reported to aid in recovery (94). It should be recalled, however, that excessively large doses of chlortetracycline can cause liver damage (95) A maximum of 1 gm of chlortetracycline intravenously, or 2 gm. orally is recommended (96). Considerably more work, however, is needed to establish the place of chlortetracycline in acute viral hepatitis. Similarly, the place of ACTH and cortisone in cases of acute viral hepatitis requires further investigation It is generally agreed, however, that the administration of both ACTH and cortisone will result in a prompt and dramatic fall in serum bilirubin when administered to patients with acute viral hepatitis. In one group studied (97, 98, 99) the administration of ACTH early in the disease was associated with a greater tendency to relapse than when given later In a control group of 220 patients not given ACTH no relapses were recorded The possibility that the group given ACTH therapy were more closely observed than the untreated cases must be considered,

particularly in the light of the high incidence of relapses in untreated patients reported by others (90). Another series of patients treated with cortisone also showed a more rapid fall in serum bilirubin than control subjects and patients given ACTH. Relapses, however, occurred in three patients receiving cortisone whereas no relapses occurred in the control subjects (98). ACTH and cortisone were also used in 11 cases of severe viral hepatitis, six of whom had a fulminant course with coma. While temporary improvement resulted in some of the cases, all six patients in hepatic coma died and no significant improvement was noted in the rest (99). However, Ducci & Katz (100) reported two consecutive cases of fulminant hepatitis and coma who responded dramatically to treatment with massive doses of cortisone. Occasional dramatic instances of recovery of patients in hepatic coma as a result of viral hepatitis following the administration of cortisone have also been seen by the authors of this review In summary, the blithe and indiscriminant dispensing of ACTH and cortisone in the average case of viral hepatitis is to be strongly condemned, and these drugs should be reserved for those patients in whom progressive hepatic destruction and coma rapidly supervene.

Special Types of Liver Disease

Biliary cirrhosis.—The classification of biliary cirrhosis into primary and secondary groups is now widely accepted (101, 102). The primary type has attracted the most interest and results from a variety of pathological processes within the liver giving rise to the signs of biliary obstruction: high bilirubin levels with relatively normal general liver function, high alkaline phosphatase, and high serum lipids and, particularly, the phospholipids. Hemochromatosis, infectious hepatitis, and arsenical hepatitis have been implicated as causative agents in a small percentage of cases of primary biliary cirrhosis (103, 104, 105) However, the great majority of cases in this group are of unknown etiology. Although the possibility that different and undefined etiological factors may be responsible for the biliary cirrhosis in these patients cannot be ruled out, considerable evidence has accumulated indicating that they may be grouped together as a single syndrome. The extremely high female incidence suggests a common etiology. The great majority of patients with biliary xanthomatosis fall into this category and the presence or absence of xanthoma has been correlated with the height and duration of the serum lipids (101). The unique distribution of serum lipids with predominant elevation of free cholesterol and phospholipids is characteristic [illegible] (101).

that methyltestosterone has benefited certain of these patients However, this agent causes an increase in jaundice in these individuals and should be employed with special care. Portal hypertension and esophageal hemorrhages represent a common late complication in this disease which may be alleviated

by portacaval anastomosis. Despite the fact that these patients may live for as long as 15 years after the onset of their illness, the disease takes a malignant course and eventually leads to death.

Cirrhosis in young females.—An unusual incidence of cirrhosis of unknown etiology in young females has been observed for a number of years (107, 108) Of a group of 26 patients below the age of 25 with cirrhosis of the liver encountered routinely in the authors' laboratory over a five-year period, 19 were females and 7 were males. Of the 7 males, 4 gave a suggestive history of infectious hepatitis, two were found to have Wilson's disease and only one case was classified as being of unknown etiology. In the female group, however, only three gave a suggestive history of infectious hepatitis; in the remaining 16 no etiology was apparent. There was no clear-cut evidence of dietary deficiency, unusual alcoholic intake, or exposure to toxic agents It appeared that there was an overwhelming female incidence of cirrhosis of unknown etiology in this young age group.

In the majority of cases the first manifestations of disease develop close to the age of puberty and amenorrhea is a common early symptom. Jaundice is a relatively late manifestation and is associated with signs and symptoms of cirrhosis of the liver rather than an acute hepatitis Manifestations of Cushing's syndrome occur in some of the patients and increased excretion of urinary corticoids has been reported (108). An unusual elevation of the total protein of the serum because of markedly increased gamma globulin levels has also been noted in some of these patients (107). A large accumulation of plasma cells in the liver of the latter cases has been observed. The presence of a severe rheumatoid type of arthritis associated with the liver disease has also been found in a number of these young females Others of this group show no unusual manifestations except those of severe progressive cirrhosis

The etiology of the cirrhosis in these young girls remains obscure. The possibility that the virus of infectious hepatitis is the causative agent producing an unusual and chronic type of disease under specific endocrine influences which exist in these young females must be considered On the other hand, the generalized manifestations of the disease in certain individuals sometimes involving the joints, the pericardium, and the lungs in addition to the liver suggest the possibility of a disease like lupus erythematosus.

Hemochromatosis.—Although the precise pathogenesis of hemochromatosis remains obscure, current work continues to shed light on this interesting disease. The occurrence of severe pain in patients with hemochromatosis is now well-recognized (109 to 112) In a series of 30 cases described by Marble & Bailey (110) abdominal discomfort was present in 11 (37 7 per cent). In some cases the pain may be sufficiently severe that it may mimic an acute abdominal catastrophe The incidence of primary carcinoma of the liver is higher in patients with hemochromatosis than in classical Laennec's cirrhosis In three separate series of cases of hemochromatosis recently reported the incidence of carcinoma was found to be about 20 per cent (110, 112, 113).

Cardiac irregularities, heart failure, and sudden death are frequent late complications of the disease and are usually associated with deposition of iron in the myocardium (114).

Although the iron binding protein is completely saturated in hemochromatosis, the serum iron level is usually normal or slightly increased. An increased level of serum iron has been reported in some patients with hemochromatosis immediately prior to death (115, 116, 117). In these cases the high level of serum iron is usually ascribed to sudden necrobiosis of liver tissue with release of iron into the circulation, an explanation which has also been advanced to explain the finding of an increased serum iron in patients with acute hepatitis (118). However, Howard and co-workers (116) have reported a patient with hemochromatosis who was not in the terminal stages of the disease who had a serum iron that varied between 7000 μg per cent and 8000 μg per cent (normal range 70 to 150 μg per cent). This value was first noted 4½ months after venesection was begun and at a time when the patient felt extremely well and experienced no toxic symptoms The authors suggest, as a hypothesis, that, although hemoglobin synthesis was rapid, it was nevertheless unable to keep pace with the rapid mobilization of the iron stores

The therapeutic value of repeated venesection in hemochromatosis has become well-established In a recent series of 15 cases so treated, 11 showed a satisfactory response (119). The distinction between transfusional siderosis and classical hemochromatosis has been the subject of a careful and critical study by Kleckner *et al.* (111) Despite the many reports in the literature of cases of hemochromatosis secondary to multiple blood transfusions (120, 121, 122) these workers consider that the two conditions should be regarded as separate and distinct entities.

Wilson's disease —This rare disease which combines cirrhosis of the liver, lenticular degeneration, and Kayser Fleischer rings has received considerable attention from a number of investigators in recent years It has become clear that the disease is inherited in a recessive fashion (123) and is associated with disturbances of copper and amino acid metabolism (124 to 128). Characteristically, a deficiency of ceruloplasmin, the copper carrying protein of serum, a striking decrease in the total serum copper concentration and an increased urinary excretion of copper are present Although the plasma amino acid level is normal, the urinary excretion of amino acids is markedly increased except in the earliest stages of the disease (129) Copper content of the tissues, particularly of the liver, brain (125), and kidneys (130), is greatly increased

Since the liver contains excessive quantities of copper, it is often assumed

the excessive hepatic deposition of copper are unrelated should not be summarily dismissed.

The hypothesis that the urinary loss of amino acids could produce an amino acid deficiency and thus hepatic cirrhosis is attractive but untenable. The significance of the aminoaciduria in Wilson's disease and its relationship to aminoaciduria occurring in other inherited disorders is interestingly discussed in a recent paper by Dent (131).

The diagnosis of Wilson's disease is usually seldom in serious doubt when hepatic and cerebral symptoms are both present. However, since occasionally hepatic cirrhosis may be the only apparent abnormality, the diagnosis of Wilson's disease should be suspected, in order that it may be excluded, in all cases of juvenile cirrhosis.

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DISEASES OF THE CARDIOVASCULAR SYSTEM (SURGERY)[1]

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The progress in the field of cardiovascular surgery during the past several years has made it one of the fastest growing interests in general surgery. It is an interesting fact that much of the fundamental information which has permitted the recent advances in this field has been available to the medical profession for several decades This information, plus the development of new concepts and of suitable instruments with which to carry them out, is responsible for much of the progress

Those who have developed new surgical methods in the treatment of mitral valvular disease, saccular aneurysms, and arteriosclerotic aneurysms have credited surgeons of 30 to 50 years ago with having made the first major contributions in the field. Souttar (1), an English surgeon, first digitally dilated the mitral valve of a patient with mitral stenosis in 1925. Despite a successful operation which resulted in symptomatic relief, Souttar was not referred further cases by his medical colleagues Although Carrel (2) and Guthrie (3) in the early part of this century reported the successful experimental use of arterial homografts, it was not until the work of Gross, Bill & Peirce (4) in 1949 that the method was shown to be technically feasible and useful in man. The Starling isolated heart-lung preparation has been used by physiologists since the turn of the century Only recently have the principles involved in this physiologic experiment been applied in an attempt to produce a temporary bypass of a patient's heart and lungs for the performance of cardiac surgery. Tuffier (5) in 1902 reported the successful treatment of a saccular aneurysm of the ascending aorta, and the technical method he employed was very little different from that used today Tuffier's error was a failure to remove the devitalized aneurysmal sac which presumably became infected and resulted in secondary hemorrhage.

The purpose of the present review is to select certain aspects of cardiovascular surgery which have been of particular interest to the writers, to outline recent advances, to indicate the present status of therapy, and to attempt to predict future developments Advantage will be taken of a reviewer's right to comment candidly, speculate freely, and present personal opinion without support of objective data We shall deal first with supportive aids in cardiovascular surgery with particular reference to the artificial heart-

[1] The survey of literature pertaining to this review covers many but not all contributions published in the period since the preceding surgical review of the cardiovascular system (July, 1949 to June, 1954) The abbreviation *et al.* is used reluctantly when more than three authors' names appear on a paper.

lung machines, to the controlled cross-circulation, to hypothermia, and to arterial homografts. Following this, we shall consider some of the specific cardiovascular lesions in the treatment of which progress has been made

SUPPORTING AIDS IN CARDIOVASCULAR SURGERY

Heart-lung machines —As cardiac surgery has developed, the surgeon has become more and more aware of the impediment offered by the necessity of his working blindly within the chambers of the heart. It has been a logical effort, therefore, to attempt to create a bloodless intracardiac operating field so that corrective surgery might be carried out with greater leisure, accuracy, and safety. Attempts to produce such a bloodless field have been the two types: (*a*) a simple pump to substitute for the function of either the right or the left ventricle, or the simultaneous use of two such pumps, the individual's lungs being used *in situ* to oxygenate the venous blood; (*b*) the pump-oxygenator which substitutes completely for the normal cardiorespiratory mechanism. Pumps of the first type have been used with considerable success in experimental animals [Wesolowski and co-workers (6); Clowes (7); Southworth *et al.*, (8)] The obvious limitation of this approach is that many congenital cardiac conditions which require surgical treatment have auricular or ventricular septal defects The presence of such a defect requires a total bypass of the heart if a bloodless field is to be achieved

The first work of Dr John H. Gibbon, Jr on the artificial maintenance of the circulation with a pump-oxygenator was reported in 1939 (9). The meticulous work of this investigator over the past 15 years on the technical problems of the heart-lung machine, and his co-operation with other workers, are in large measure responsible for recent rapid advances Gibbon's early experiments showed that 4 min of pulmonary artery occlusion in an attempt to obtain a bloodless heart produced irreparable neurologic damage, and 10 min. occlusion produced death Employing his early heart-lung machine, he was able to report the first prolonged survival of animals following total mechanical bypass, using a pump and oxygenator Employing similar machines, a number of investigators have successfully substituted temporarily for the heart and lungs in dogs [Miller, Gibbon & Gibbon (10), Jongbloed (11), Dennis and co-workers (12); Dodrill, Hill & Gerisch (13), Helmsworth and co-workers (14)] Although the procedure is technically possible, the mortality rate is high enough to preclude unrestricted application to man

The mechanical oxygenator is responsible for many of the difficulties To expose a quantity of blood equivalent to a normal cardiac output to an oxygenated atmosphere without hemolysis or air embolism is a formidable task. Some investigators have attempted to circumvent this difficulty by employing homologous lungs as an oxygenator [Potts and co-workers (15); Mustard, Chute & Simmons (16), Mustard & Chute (17), Fischer and co-workers (18), Wesolowski, Fisher & Welch (19)] Wesolowski, Fisher & Welch (19) have obtained five consecutive survivals following total substitution for the heart and lungs of dogs over a period of 2 hr Gollan and co-

workers (20, 21) have reported the use of hypothermia in conjunction with a pump-oxygenator to reduce cardiac output requirements of the mechanical system. These investigators report the survival of 15 consecutive animals following a 1 hr. bypass (21).

Until the present time only a few attempts have been made to perform cardiac surgery in man with the help of such an artificial circulation. Dennis and co-workers (12) have reported an unsuccessful attempt to close an atrial septal defect. Failure was attributed to excess citrate in the transfusions which were required to replace a large and unanticipated blood loss. Dodrill, Hill & Gerisch (22) have reported a successful left ventricular bypass. The superior pulmonary vein and the subclavian artery were cannulated and blood was diverted from the region of the mitral valve at a rate of 4½ liters per min for a total time of 50 min. It had been planned to attempt surgical repair of an insufficient mitral valve, but technical difficulties prevented the carrying out of the procedure. More recently, Dodrill (23) has reported several isolated right- and left-sided bypasses as well as a bilateral bypass in an 18 year old girl with pulmonic stenosis The latter patient was carried on an artificial heart for 35 min. Death occurred on the fourth day as a result of atelectasis and brain damage. Gibbon (24) has successfully closed an atrial septal defect employing total substitution for the heart and lungs.

Although it has been demonstrated to be technically feasible to make use of a mechanical substitute for the heart and lungs in man, the development of this technic has not reached the point where it may be considered a generally acceptable procedure Physiologic problems concerned with hemolysis, regulation of blood flow and volume, shock, and air embolism are not totally solved and are major causes of death. The high mortality associated with the procedure would seem to limit its use, at least for the present, to cardiac defects which cannot be corrected by other means and which are likely to lead to the patient's death at an early time It would not seem justifiable to employ such machines to perform surgery for conditions such as mitral stenosis and pulmonic stenosis for which the present procedures, although not ideal, are satisfactory and have a low operative mortality. It seems likely, however, that in the near future heart-lung substitution will permit the treatment of ventricular septal defects as well as other anomalies for which at present there are no satisfactory methods of therapy.

Controlled cross-circulation —Several investigators have used cross-circulation to permit surgery on the open heart By connecting the arterial system of a donor animal to that of the recipient animal, the heart and lungs of the former can be made to perfuse the peripheral tissues of both animals. It is

were regularly able to obtain survival in dogs by use of an improved procedure These investigators found that a high donor mortality could be avoided by placing a controlling pump between the circulation of the two animals.

Such a pump regulates the cross-circulation and maintains constant the blood volume of each subject. The recipient animal works at a reduced peripheral blood flow, which, however, is adequate to maintain life. This technic has been employed in man by Warden and associates (27), although the details and results are not as yet available in the scientific literature There are theoretical objections to the use of the donor circulation method. The procedure is not without danger to the donor and some difficult emotional and ethical problems may be encountered in obtaining a donor for a patient who requires intracardiac surgery.

Hypothermia.—The use of reduced body temperatures as an adjunct to cardiac surgery has been stimulated by the work of Bigelow (28 to 31) and Boerema (32) and their associates The fact that man can survive prolonged periods of hypothermia was apparent from the survival of an occasional patient exposed accidentally to prolonged cold. Physiologists have long known that there is a reduction in body oxygen consumption of about 7 per cent for each degree centigrade that the body temperature is lowered There are two applications of this observation to cardiac surgery: (*a*) in a state of reduced metabolism it is possible to carry out a more prolonged interruption of the circulation without producing neurologic damage, (*b*) body cooling can be used to reduce the oxygen requirement of cyanotic individuals undergoing surgery. Relatively minor degrees of cooling have usually been employed for this latter purpose.

The use of the circulatory interruption technique under hypothermia has been the subject of vigorous investigative effort in a number of clinics, and already there are many case reports of its successful use. Cooling of the individual is accomplished by exposure, immersion in cold water, packing in ice, wrapping in a circulating ice water blanket, by passing arterial blood through cooling coils, or by irrigating the open chest with cold saline solution. The operative technique consists of occlusion of the superior and inferior vena cavae, myocardotomy, performance of corrective surgery, closure of the heart incision, and restoration of the circulation Rewarming is accelerated by immersing the subject in warm water or by the use of a radiofrequency induction coil, as described by Bigelow, Callaghan & Hopps (28). Early work on animals with this method produced an occasional long-term survival, but many animals died of ventricular fibrillation at the time of surgery or of postoperative shock (28). Working with dogs, Cookson, Neptune & Bailey (33) were able to obtain an 80 per cent survival rate with 12 min. circulatory occlusion with the help of piperoxan (Benodaine), thiamine, intravenous glucose, morphine, atropine, pentothal, digitoxin, methoxamine (Vasoxyl), penicillin, and ACTH.

Ventricular fibrillation during hypothermia has proven to be, in the hands of most investigators, intractable to the usual electric shock therapy. Contrary to the experience of other investigators [Swan *et al.* (34); Zeavin, Virtue & Swan (35), and the writers], Bailey and associates (36) have found that electric shock is much more effective in defibrillating the heart during

hypothermia than at normal temperatures The careful physiologic studies of Swan and co-workers (37) suggest that alterations in serum potassium, pH and CO_2 are responsible for the increased incidence of ventricular fibrillation. These workers have developed a technique which accomplishes defibrillation of the heart in both animals and man by the injection of potassium. Although the mortality rate with hypothermia in early experiments was prohibitively high, better results are being achieved as more fundamental information is obtained Many groups of investigators have added valuable data on the effect of lowered body temperature on cardiac output, blood pressure, oxygen dissociation, pulse, hematocrit, hemoglobin, and serum electrolytes (38 to 47).

The major difficulties encountered in the clinical use of hypothermia have followed closely the pattern numerous investigators have noted in the experimental animal. Bailey and associates (36, 48) encountered an operative mortality of 69 per cent in the 16 patients on whom they operated In all fairness, it should be emphasized that the lesions for which they were operating were extremely serious ones, for example, their series included a number of cases of transposition of the great vessels, a lesion which has a very high operative mortality. They point out that the technique can be justifiably applied only to lesions for which there is no other applicable method of therapy Kaplan, Helmsworth & Clark (49) have reported the use of hypothermia in a series of infants Seventeen of these children were cooled for diagnostic procedures such as angiocardiography, aortography, and cardiac catheterization. Nine infants were cooled for operative procedures which included ligation of a patent ductus arteriosus and performance of systemic-pulmonary shunts. The authors conclude that reduction in body temperature in children with severe congenital heart disease considerably reduces the risk attending surgical procedures and specialized investigations The mortality associated with the diagnostic procedures is so low that many (50) feel that physiologic alterations associated with body cooling would be more dangerous than the diagnostic procedure itself. It is interesting to note that the young of a species tolerate hypothermia better than do adults Early clinical experiences tend to confirm this observation

Among the best clinical results that have been achieved with hypothermia are those of Swan & Zeavin (51) Of their patients operated upon for atrial septal defects, tetralogy of Fallot, and isolated pulmonic stenosis, 14 of 16 survived the operative procedure These excellent results may be attributed in large measure to the carefully planned and controlled series of animal experiments in which these investigators studied the fundamental physiologic changes associated with hypothermia Lewis & Taufic (52) have also successfully closed atrial septal defects with circulatory interruption under hypothermia

In addition to its use in permitting prolonged interruption of the circulation, hypothermia has been employed as an adjunct to surgery in severely cyanotic children. This cooling is frequently only to the extent of several

degrees centigrade. Although the theoretical advantage is therefore less, the morbidity and mortality are also less. Riker (53) has cooled severely cyanotic children several degrees to improve oxygenation during operation Muller (54) has also employed hypothermia as an adjunct to surgery without cessation of circulation in 22 children.

A recent editorial in *Lancet* (50) lends the following note of caution regarding hypothermia:

> ... to the surgical treatment of ... his would as yet hardly seem ... thout hypothermia in many thousands of cases, with so low an immediate ... y as to suggest that in most cases reduction of body temperature may enhance rather than decrease the risk. . . . In very serious cases where a high operative mortality is to be expected, there may be some justification for cooling, but the wish to assess the practical value of this new method should not obscure the possibility that there is no real need for it.

We think that the opinions expressed in this editorial are sound

We have used hypothermia during operations on a few severely cyanotic infants. Convincing evidence that the results are better than those without hypothermia has not been obtained We wish to make it clear that we are referring here to severe reductions in body temperature and not to mild depressions as used by Riker (53) and others Severe hypothermia should not be used in operations on patients in whom the desired result can be obtained without its employment

Arterial homografts—There was an interval of about 40 years between ... grafting and its ap- ... no- grafts followed storage of the arterial segment ... ce's solution at 0°C Gross and his co-workers employed a buffered nutrient medium which maintained the viability of the tissue for several weeks, as dem- ... in obtaining grafts from previously ... rage period is wasteful of valuable arterial segments Therefore, several methods have been developed to prolong the period of storage These include preservation by formalinization (55, 56), quick-freezing (57, 58, 59), or lyophilization (60, 61, 62). The early work of Gross and his co-workers (4) indicated that the demonstration of the ... attribute of the method of ... peared an impressive series of studies with evidence to the contrary ... e & Blades (63) found that viability had no effect upon the success of the transplant MacPherson and associates (64) found similar results in that under their experimental conditions the function and fate of the arterial graft had no apparent relationship to tissue culture viability tested at the time of grafting Deterling, Parshley & Blount (59) noted, when a comparison of the nutrient and quick-freeze

methods was made, that the degree and type of histopathologic change was the same. The studies of Pate & Sawyer (65) give evidence to indicate a superiority of the lyophilization over the nutrient medium method Since it is known that viability does not persist in homografted tissues, it must be admitted that there is a certain logic to the point of view which maintains that viability is not necessary for successful arterial homografting. Histologic studies show that the homografted artery actually serves as an inert and nonviable blood conduit which is eventually invaded and replaced to a greater or lesser extent by host tissue [Bellman & Gothman (66); Bencini & Bellinazzo (67); Miller *et al.* (68)]. The recent trend, therefore, has been toward the use of nonviable homografts and inert prosthetic materials such as Vinyon "N" [Voorhees, Jaretzki & Blakemore (69)].

Although arterial autografts represent ideal blood vessel replacement and are indistinguishable from normal arteries following grafting [Miller *et al.* (68)], the sacrifice of another artery of adequate size in clinical cases is ordinarily not possible Autogenous vein grafts have been used successfully to bridge arterial defects in man [Cooke and co-workers (70)] However, long term follow-up on the experimental use of vein grafts for the replacement of aortic segments has shown a disturbingly high incidence of dilatation and aneurysm formation [Schmitz *et al.* (71); Nabatoff *et al.* (72)]

Our own experience with the lyophilization, or "freeze-dry" method, has been most satisfactory Following the technique of Pate and co-workers (65) and Hufnagel (73), the fresh arterial segments are placed in glass cylinders, frozen quickly in carbon dioxide-ether slush, and then lyophilized The dehydration procedure consists of subliming the frozen water in the tissue to the gaseous state under high vacuum. The grafts are then sealed under vacuum in the original tubes and stored until needed. Brown and co-workers (62) found that grafts so prepared show no evidence of deterioration at the end of two years At the time of use, the grafts are immersed in saline solution for rehydration, after which they have the appearance of fresh artery. Our clinical experience has been in keeping with that of Marrangoni & Cecchini (61) who found that lyophilized grafts were uniformly successful, at least in the aorta, provided that no bacterial infection occurred

The studies of Gentsch, Waters & Glenn (74) are of interest in regard to the long-term results of homologous aortic grafts These investigators, working on dogs, produced a hypervolemic-lipid stress by the injection of a lipid emulsion, thus producing lipemia and elevation of the blood cholesterol. Compared to the animal's normal artery, the homograft showed a fatty infiltration and calcification having many of the features of arteriosclerosis Their study is a sobering reminder that the long term fate of homografts cannot be predicted on the basis of immediate success.

In our own clinic several dozen freeze-dried grafts have been employed in the treatment of arteriosclerotic aneurysm In such cases there is little concern over the long term results of the graft, since the life expectancy of

patients in the fifth, sixth, and seventh decades is not likely to put the longevity of the graft to a test. We have been considerably more concerned over the use of homografts in the repair of coarctation of the aorta.

As reported by Sloane (75), we have been able to accomplish a direct end-to-end aortic anastomosis in approximately 90 per cent of cases of coarctation of the aorta. An additional 5 per cent could be treated through the usual incision with the aid of a homograft. Recently Gross (76) has reported grafting 19 of 180 patients, the majority of these grafts being placed in the last 120 cases Gross has emphasized the necessity of obtaining a full-sized aortic lumen and points out the facility with which a graft can be used to replace a widely resected area of coarctation. How such grafts will function after 10 or 15 years is a question which must be answered by time. Certainly the grafts which were placed by Gross, Bill & Peirce (4) more than five years ago have thus far fully justified the confidence placed in them. Because of questions concerning the ultimate fate of homografts, we prefer an aortic lumen that is slightly smaller than normal in size to a larger one that is obtained by the use of a homograft

We turn now to a consideration of specific cardiovascular lesions

Specific Lesions

Aneurysms—Since Valisnari's patient with an abdominal aneurysm was treated by lancing in 1719 (77), aneurysm of the aorta has been a major surgical problem At the turn of the century, Tuffier (78) stated that aneurysms of the aortic arch to be amenable to surgery must be "accessible, isolable, and extricable " Following a careful anatomic and pathologic study of available specimens, Tuffier planned and carried out the first isolation of an aortic aneurysm in 1902 Unfortunately, the patient died in the late postoperative period from secondary hemorrhage. Several other unsuccessful attempts to excise aortic aneurysms at about this time diverted surgeons to attempt less heroic (and less definitive) methods of treatment. These methods include proximal ligation of the involved vessel [Babcock (79)], the insertion of heated wire to produce clotting [Blakemore (80)], wrapping with fibrogenic and reinforcing materials [Cowley & Yeager (81)], and many others The results of all of these have been disappointing.

The therapy of aortic aneurysms in the past several years has advanced along two lines depending upon the nature of the lesion, whether syphilitic or arteriosclerotic Syphilitic aneurysms are usually saccular in shape, occur in the thoracic aorta, are likely to erode vital structures, cause severe pain, occur in middle age, and are associated with a life expectancy which may be measured in weeks or months On the other hand, arteriosclerotic aneurysms are usually fusiform in shape, are seldom located above the renal arteries, rarely cause bone erosion, and have a somewhat better prognosis [Bahnson (82)]

Although there have been sporadic reports of successful treatment of saccular aneurysms, it remained for Bahnson (83) and Cooley & DeBakey

(84) to establish excisional therapy as the definitive treatment of these lesions. Bahnson reports the successful excision of the sac and suture of the aorta in six of eight patients in whom the operation was attempted.

In 1951 Dubost, Allary & Oegonomos (85) reported the excision of a fusiform aneurysm involving the bifurcation of the aorta and replacement with an aortic homograft. DeBakey & Cooley (86) more recently have reported a remarkable series of 13 patients (now much larger) treated by resection of the aneurysm and restoration of aortic continuity by homograft with only one postoperative death. This low mortality figure is all the more noteworthy when it is considered that most of the patients were in the sixth and seventh decades of life. Bahnson (87) reports a series of 14 patients undergoing excision and grafting of an arteriosclerotic aneurysm, with only one operative death.

In summary, excision has been established as a definitive therapy of saccular aneurysms of the thoracic aorta in view of the average life expectancy of such patients of from six to nine months [Kampmeier (88)] The indications for surgery in the elderly patients with arteriosclerotic aneurysm are somewhat less clear-cut. Estes' figures indicate that, whereas 65 per cent of a normal population aged 65 survive for eight years, only 10 per cent of those having abdominal aneurysms survive for a similar period of time (89). Sixty-three per cent of the patients in his series died from rupture of the aneurysm. The presence of symptoms seems to be the major indication for operation and the procedure can be carried out with what may be considered a very acceptable operative risk

Constrictive pericarditis—Holman & Willett (90) have introduced a new concept in the treatment of constrictive pericarditis by advocating surgical intervention during the acute stages of tuberculous pericarditis. The availability of anti-tuberculosis drugs may bring about a radical change in our present concepts of the surgical treatment of this disease Holman & Willett (91) have emphasized the necessity of decorticating not only both ventricles but the atria and venae cavae as well. On the other hand, Scannell, Myers & Friedlich (92) find that systemic venous hypertension in this syndrome is relieved by ventricular decortication without lysis of the right atrium or great veins The experimental work of Isaacs, Carter & Haller (93) lends strong support to the position taken by Scannell and his co-workers. Isaacs and his associates produced localized as well as generalized constriction of all parts of the pericardium in experimental animals Decortication was then carried out in selected areas and it was demonstrated that the essential feature of the operation consists of decortication of the ventricles

The writers find that decortication of both ventricles can be performed satisfactorily in patients by exposure through a long left anterolateral transpleural incision through the fourth interspace with division of the fourth and fifth costal cartilages. The results are superior to those obtained when the exposure was inadequate.

Mitral stenosis—In 1902 Sir Lauder Brunton first appreciated that mi-

tral stenosis was a mechanical lesion which might be attacked surgically (94). As noted previously, Souttar successfully dilated a stenotic mitral valve via the left auricular appendage in 1925. Souttar's feat was apparently an anachronism, for his medical colleagues were not yet prepared to refer their patients for an operation "directly upon the heart." Such a fruitful lead as Souttar's would today be vigorously followed by groups of investigators the world over. Under the stimulus of the work of Bailey and of Harken great advances have recently been made.

The diagnosis of mitral stenosis is based upon physical signs plus a symptom complex resulting from the elevation of pulmonary venous pressure behind a stenotic mitral valve In the early days of this operative procedure, cardiac catheterization was an aid in the diagnosis, but, more specifically, permitted objective evaluation of operative results. At the present time it is considered unnecessary in diagnosis except in the unusual cases. The symptoms and signs of mitral stenosis may consist of cough, dyspnea, hemoptysis pulmonary congestion, atrial fibrillation, and the characteristic mitral murmur. There seems to be general agreement that acute rheumatic activity and subacute bacterial endocarditis represent contraindications to operation. Marked enlargement of the left ventricle is considered indicative of a severe degree of mitral insufficiency and is thought by most to rule out operation [Andrus (95); Glover (96)] Intractable right heart failure and multivalvular disease are also considered by some to be contraindications to operation The presence of severe aortic stenosis, formerly a contraindication to operation, is now an indication for combined mitral and aortic commissurotomy [Bailey (97), Glover (96), Johnson *et al.* (98)] Most surgeons have required that the predominant mitral lesion be stenosis Commissurotomy can be carried out with some relief of symptoms in the presence of a degree of mitral insufficiency, but the results in this group of patients are not as satisfactory as in those having pure stenosis. Direct inspection by palpation of the function of the mitral valve at the time of operation has resulted in a more cautious interpretation of what were once considered infallible auscultatory signs For example, Glover and associates (99) found pure mitral stenosis in 97 cases, even though ⅓ of this number were considered to have mitral insufficiency on the basis of preoperative auscultation of the heart.

In our experience, commissurotomy can be performed satisfactorily by finger-fracture or tear in approximately 80 per cent of cases. In those instances in which this cannot be accomplished, we usually use a Brock knife or a Dubost dilator Some surgeons use an instrument rather than the finger in a much larger proportion of cases

The functional results of the operation are excellent and the operative risk is low. In general, the operative mortality has been between five and ten per cent [Cooley & DeBakey (100); Glover (96)]. In most series 75 to 80 per cent of the patients are improved, as evidenced by increased exercise tolerance, disappearance of dyspnea and orthopnea, cessation of embolization and disappearance of cough and hemoptysis. Physiologic studies show that

there is an increased cardiac output, decreased pulmonary arterial hypertension, decreased pulmonary vascular resistance, and a fall in left atrial pressure [Andrus and associates (101, 102); Werko *et al.* (103)]. The symptomatic improvement is usually greater than the alteration in the physiologic measurements.

One of the most distressing complications of operation is the occurrence of embolism, either from mural thrombi or from calcium flecks located on the valve surfaces. Such embolism is a major cause of operative mortality [Andrus, Blalock & Milnor (101); Bolton, Maniglia & Massey (104); McGoon & Henly (105)] Various measures, such as entering the atrium through a pulmonary vein and the temporary occlusion of the carotid arteries, have been employed in efforts to prevent embolization None, however, has been entirely satisfactory. Despite the danger of emboli during operation, the relief of atrial stasis by commissurotomy is apparently effective in preventing spontaneous emboli in the late postoperative period.

Brock (106), Cooley & Chapman (107), and Sellors, Bedford & Somerville (108) have pointed out the facility and safety with which mitral commissurotomy can be performed during pregnancy. On the other hand, Burwell's experience with 300 pregnant women with heart disease at the Boston Lying-in Hospital supports the opposite point of view (109). The latter, in his earlier experience, referred patients for operation during pregnancy. At the present time, however, he believes that the best interests of both mother and child are usually served by careful medical management with postponement of commisurotomy until post partum.

Sabiston & Follis (110) and McNeeley, Ellis & Harken (111) have shown a high incidence of Aschoff bodies in left auricular appendages biopsied at the time of operation There appears to be no correlation between such Aschoff bodies and the usual clinical manifestations of acute rheumatic fever. The appearance of such pathologic lesions after many years' absence of clinical signs of rheumatic fever undoubtedly represents important information on the natural history of rheumatic disease As yet, however, no one has been able to give a satisfactory interpretation of the significance of these lesions.

In general it may be stated that the surgery of mitral stenosis is in a satisfactory state It is to be hoped that the long term results will support the present optimism Unfortunately, the surgery of mitral insufficiency is still in the experimental stage

Aortic stenosis —Among the other pioneering firsts of the French surgeon Tuffier was his attempt in 1912 to treat aortic stenosis surgically (112) At that time Tuffier believed that the most logical approach for the surgical division of the fused cusps of the aortic valve was with a transaortic knife passed retrogradely Because experimental evidence was lacking to justify such a procedure, Tuffier is said to have manually dilated the aortic valve by invaginating the wall of the aorta just above the base of the heart It is difficult to believe that a stenotic valve could be satisfactorily dilated by this method Sporadic attempts in the past five or six years have been made by a number

of surgeons to dilate, cut, or tear the fused aortic valve by passing an instrument through the left ventricular myocardium and up the aortic outflow tract. The results have been much better since Bailey, Redondo-Ramirez & Larzalere (97) developed a rugged dilator with a probe finder and an expandable head which is passed through the wall of the left ventricle and opened after it reaches the stenotic area. There was an 18 per cent mortality in the early cases treated by this method. Glover (96), in a series of 22 cases, had an operative mortality of 12 per cent in isolated aortic stenosis, provided that intractable congestive failure was not present. The mortality was considerably increased in the presence of simultaneous mitral surgery. His results in the treatment of aortic stenosis once congestive failure had become permanent were so poor that he considers such failure a contraindication to operation. Attempts have been made by Brock (113) and Bailey *et al.* (114) to approach the aortic valve via the arterial system. Bailey *et al.* have reported a method employing a rubber diverticulum of the type described by Glenn (115) for intracardiac surgery. The diverticulum is sutured to the ascending aorta and the aortic valve is dilated by an instrument introduced through this diverticulum. However, the technical difficulties of such an operative approach appear to exceed those encountered in the left ventricular operation.

Real progress has been made in the treatment of aortic stenosis It appears likely that the results will be even better when the technical methods are improved further.

Aortic insufficiency—As has been true with surgery of mitral insufficiency, the insufficient aortic valve has presented a more difficult problem than aortic stenosis The signal contribution in this field is the technical feat of Hufnagel (116). He has constructed a ball-valve type plastic prosthesis which can be inserted into the descending thoracic aorta. The use of such a valve prevents regurgitant flow through the aortic valve from at least the lower half of the body. The technical problems concerned with inserting such a prosthesis in the ascending aorta have not yet been solved. There is some doubt whether such a location would be acceptable, since under these circumstances coronary filling during diastole would be at the very low left ventricular filling pressure, rather than at systemic pressure. Hufnagel now has a series of cases treated with this prosthesis with an acceptable mortality and satisfactory early operative results (117).

Coronary artery disease—The leading place which coronary insufficiency holds as a cause of death is adequate justification in itself for the many attempts which have been made to treat this condition surgically. The pioneering and persevering work of Dr. Claude Beck deserves special mention. Beck's efforts have been directed along two approaches to the problem of increasing myocardial blood supply: (*a*) The stimulation of collateral circulation and of intercoronary communications by abrading the epicardium and placing tissues such as pectoral muscle against the myocardium, and (*b*) the direct anastomosis of a systemic artery to the coronary venous system.

Thompson & Plachta (118) have recently reported their experience over a fourteen-year period with "cardiopexy" in the treatment of coronary artery disease. These investigators have produced a granulomatous pericarditis by the instillation of talc within the pericardium. Fifty-seven patients so treated have been followed from 1 to 14 years The operative mortality was 12 per cent. These investigators feel that the average duration of life following first symptoms, in those patients whose cases have been followed to death, is approximately twice that of those treated without operation. Vineberg (119) has employed implantation of the internal mammary artery into the left ventricular myocardium. Three of his four patients survived and appeared to be benefited. Neumann and his co-workers (120) have presented evidence that pedicled grafts of skin and subcutaneous tissue develop good collateral circulation with myocardium against which such pedicles are implanted. Their experimental work in dogs demonstrates that such a collateral vascular supply protects animals after ligation of a left descending coronary artery, a procedure which ordinarily has a 70 per cent mortality.

Beck and his co-workers (121) have reviewed the clinical results of their systemic-coronary anastomosis. This procedure connects by means of a homograft the aorta with the coronary sinus at the first stage of a two-stage operation. At the second operation, performed some weeks later, the mouth of the coronary vein is constricted so that some of the systemic blood entering the coronary vein is forced to flow in a retrograde direction. The rationale of this procedure is to produce retrograde perfusion of the myocardial capillary system. Twenty-eight patients have been operated upon with 23 recoveries and five deaths Of the 23 recoveries, 13 patients had both stages of a two-stage operation In the remainder it was technically not feasible to complete the operative procedure.

Bailey, Bolton & Likoff (122) have employed this procedure in man and state: "Obviously a reversed blood flow in the coronary sinus would inevitably enter the myocardial capillaries since they are developmentally in direct communication with the ultimate ramifications of the tributaries of the coronary veins " A survey of the physiologic literature reveals that the opinion of a number of investigators is at variance with this point of view Since the coronary venous system is not an "end circulation" (123) there are many who believe that the shunted blood passes out through the coronary thebesian system without actually entering the myocardial capillaries Experiments with the capillary bed of the dog's intestine have shown that it is possible to reverse blood flow temporarily in the smaller mesenteric vessels, but that such reversal persists only for a short period of time [Heimbecker, Thomas & Blalock (124)] The results of the experiments of Eckstein and his associates (125) indicate that significant retrograde perfusion of the myocardium after the Beck operation persists only for a period of about five weeks. During this time, however, there is definite protection against experimental coronary occlusion.

The experimental and early clinical work in this field has been sufficiently

encouraging to justify further effort. A careful objective evaluation of the functional results following operation seems desirable if further progress in this field is to be made. Recent discoveries in the fields of lipid metabolism and the genesis of arteriosclerosis offer the hope that coronary disease may be prevented, rather than treated after it develops

Patent ductus arteriosus.—The patent ductus arteriosus problem was so completely solved by Gross (126) that little has been added in the past decade. Long term follow-up of the patients operated upon indicates that, provided the ductus was uncomplicated by other anomalies, the patients lead a normal life thereafter. Recurrence of the ductus following ligation or division is extremely rare and is usually the result of bacterial endocarditis at the site of the ductus An analysis of 500 of our cases shows an operative mortality of 3 per cent. Most of these deaths occurred in patients with an erroneous preoperative diagnosis (127) It is worthy of note that 11 per cent of this series of cases did not have the typical continuous murmur which is generally considered characteristic of this anomaly These patients usually have a large ductus and pulmonary hypertension It is essential that this group of patients not be overlooked so that they may receive the benefit of operation.

Interatrial septal defects—A defect in the interatrial septum results in a shunt of blood from the left to the right atrium The high pulmonary blood flow resulting from such a shunt may lead to a characteristic syndrome pulmonary vascular changes, pulmonary arterial hypertension, right-sided heart failure, and eventually reversal of the shunt and cyanosis. The simple and mechanical nature of an interatrial septal defect makes this anomaly a stimulating challenge to the surgeon

There have been several general approaches to the surgical therapy Invagination of the auricular wall to create a plug for the septal defect has been used by several investigators [Cohn (128); Murray (129); Swan (130); Bailey (131)] Prosthetic materials have been used alone or in combination with this method to close the interatrial communication [Martin & Essex (132); Swan (130); Hufnagel & Gillespie (133)] A combination of hypothermia and temporary clamping of the vena cavae permits the heart to be opened for a direct closure of the defect [Lewis & Taufic (52); Swan *et al* (34)] A mechanical heart-lung machine has been used by Dennis *et al* (12) and by Gibbon (24) to permit closure of the defect in a bloodless heart The hazard of all of these procedures is considerable, and none of them may be considered a definitive answer to the problem

A unique method has recently been described by Watkins and associates (134) for experimental animals, and later applied to man by Gross *et al* (135) In this technique a rubber cylinder or "well" is sutured to the right atrium The atrium is then opened at the bottom of this well and blood rises within the well to a height determined by the central venous pressure (usually about 10 to 15 cm.) This permits the surgeon to work within the heart and close the defect either by direct suture or by sewing a piece of plastic material over the defect. Gross & Watkins (136) report 12 patients operated

upon by either the well technique or by suturing the edge of the septal defect to the atrial wall. Seven of the patients survived and five died.

Recently, Bjork & Crafoord (137) have experimented with a modification of Söndergaard & Husfeldt's method (138) of closing interatrial defects A dissection is made in the natural groove formed by the interatrial septum. This permits a purse string suture to be placed in the atrial wall in what would normally be the anatomic division between the two atria When the suture is tied, the atrial wall is concentrically compressed in such a way that the atrial chamber is divided into a non-communicating right and left half. After a series of animal experiments were performed, Björk & Crafoord applied the method to patients and have had three consecutive successes. Söndergard & Husfeldt have also successfully applied the method to man.

In view of the relatively benign course of patients with this congenital anomaly, and considering the high operative mortality which has been associated with the operation, it is difficult to establish proper indications for surgery. We have been most impressed with the dramatic clinical improvement of patients in whom the operation has been successful. On the other hand, the high operative risk in a disease which may be compatible with a relatively long life has deterred us from recommending operation except in the presence of incapacitating or progressing cardiac symptoms. Perhaps this condition will eventually be treated with the use of a heart-lung machine which permits an unhurried, accurate closure of the defect in the interatrial wall. At the present time, the mortality associated with such machines is too high to justify their use in the treatment of the average case of atrial septal defect.

Interventricular septal defects.—One of the ultimate aims in the development of the artificial circulation and hypothermia techniques is to permit an attack on interventricular septal defects Bailey and his associates (139) have reviewed their experimental and clinical attempts at correction of these defects and it is their feeling that the present methods are not entirely satisfactory. Selzer (140) summarizes the present status of the interventricular septal defect problem as follows

> The small interventricular septal defect with an insignificant shunt produces no important cardiac changes and little prospect of cardiac disability In this syndrome, surgical intervention will be justified only if and when the safety of the operation is so high that the mortality figures fall below the rather slim probability of death from therapy resistant bacterial endocarditis

There are, however, many interventricular defects which do produce symptoms It is in the treatment of these that Warden and associates (27) are making use of the controlled cross-circulation in performing closure under direct vision

Isolated pulmonic stenosis.—Pulmonic stenosis, unaccompanied by a ventricular septal defect or overriding aorta, is a relatively rare anomaly. About two-thirds of these patients have an associated patent foramen ovale which

encouraging to justify further effort A careful objective evaluation of the functional results following operation seems desirable if further progress in this field is to be made. Recent discoveries in the fields of lipid metabolism and the genesis of arteriosclerosis offer the hope that coronary disease may be prevented, rather than treated after it develops.

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Dammann & Longmire (153) have employed the direct attack method in a series of six cases in which only one patient had an excellent result. These authors conclude that the systemic pulmonary anastomosis is preferable to incision of the stenotic infundibulum because an adequate blood flow through the stenotic area was not achieved. However, they point out the theoretical soundness of the direct attack and indicate that improved technique may well produce better results. The anatomical studies of Johns and associates (154) and Donzelot and co-workers (155) indicate that many patients are unsuitable for the direct attack since they have pulmonary atresia or a complex anomaly of the pulmonary outflow tract which makes excision of the stenotic area difficult or impossible. Johns and associates found that the mortality of the procedure was higher and the results poorer than with the systemic-pulmonary shunt. On the other hand, Brock clearly points out that the mortality progressively decreases and the quality of the results increases with additional experience with this procedure. A careful followup of the operative results will perhaps indicate which method is preferable. Campbell, Deuchar & Brock (156) have presented such evidence, and it suggests that there is little difference in the results of the anastomotic procedure and the direct attack With the advances that are being made in heart-lung machines and hypothermia, it is possible that both methods will be supplanted by a more definitive type of surgery. For example, Scott (157) recently closed a ventricular septal defect and dilated the pulmonary outflow tract in a case of tetralogy of Fallot, employing total circulatory interruption for eight min. under hypothermia.

Summary

The expanding scope of cardiac surgery is apparent when one reviews the remarkable number of fundamental contributions to this field within the past several years. It is encouraging to note that there is no longer a delay of many years between the development of new principles in the experimental animal and their employment in man In the application of new operative techniques to man for the first time, the physician must carefully weigh operative mortality and morbidity against his knowledge of the natural history of the disease being treated If the attitude of the physician toward new procedures is cautious and considered, but at the same time progressive, cardiovascular surgery will continue to advance as it has during the past several years

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permits a right to left shunt and causes cyanosis. These cases are usually distinguished from pulmonic stenosis associated with tetralogy of Fallot on the basis of a marked pulmonic systolic thrill, poststenotic dilatation of the pulmonary, artery and a rather typical radiographic appearance of the heart The transventricular pulmonary valvulotomy described by Brock (141) and by Sellors (142) has been almost universally adopted as the method of choice in the treatment of these cases A number of surgeons have reported good results with this technique [Galligan, Adams & Jargens (143); Lurie & Shumaker (144); Potts *et al* (145); Humphreys *et al.* (146); Blalock & Kieffer (147)]. Hosier, Pitts & Taussig (148) have summarized the experience in our own clinic in the surgical treatment of 78 patients with valvular pulmonic stenosis with intact ventricular septum The operative mortality was about 8 per cent. Clinical improvement, particularly in exercise tolerance, was excellent. Postoperative catheterization showed that although the right ventricular pressure did not return entirely to normal, there was a progressive fall during the first year or two in the postoperative period. The operative procedure may be criticized in that it is performed blindly with only moderate control and accuracy However, there seems little doubt that the patients experience excellent relief of symptomatology at a relatively low operative risk. It is our personal feeling at the moment, and this is perhaps unjustified, that hypothermia and the heart-lung machines carry with them too great a risk to justify their use as a substitute for this relatively simple operation which produces such good results

Tetralogy of Fallot—Sufficient time has now elapsed to permit a long-term follow-up on the results of the systemic-pulmonary shunting procedure for the relief of cyanosis and disability in this condition. Taussig and associates (149) have reported a one- to six-year follow-up on 1000 cases operated upon for pulmonary stenosis and atresia Of those in whom the preoperative diagnosis was tetralogy of Fallot, it was found that 15 per cent died while in the hospital, that 2 per cent died in the ensuing eight months, and that 78 per cent obtained a good result During the period over which their study extended, there were only 22 cases of subacute bacterial endocarditis with four deaths Campbell & Deuchar (150) have reported the results of 200 shunting procedures performed by Brock, Sellors and Hill They found an 8 per cent mortality with 75 per cent of the patients so benefiting that they could walk a mile or more and lead lives that were almost normal.

The major recent contribution in this field has been the development by Brock (151) of a technique of direct attack on the stenotic area in the pulmonary outflow tract This procedure has in its favor a theoretical soundness in that it not only increases pulmonary blood flow, but may reduce the right to left shunt which ordinarily occurs through the ventricular septal defect. Glover, Bailey & O'Neill (152) have also stressed the advantage of the direct attack method over the systemic arterial shunt in that the former does not add the danger of an additional cardiac anomaly (artificial ductus). Muller,

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THE LEUKOCYTES AND THE LEUKOPATHIES[1,2]

By William N. Valentine
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Introduction

Early investigations of the leukocytes and the leukopathies centered largely around numerical and morphological variations in the peripheral blood Later, the widespread use of marrow aspiration and lymph node biopsy called attention to the value of these procedures in understanding and diagnosing the leukopathies. Still more recently efforts have been made to investigate the intracellular biochemical and enzymatic machinery present in the leukocytes and its derangement in disease The physiology of leukocytes in health and disease has been the subject of widespread investigation relating to leukocyte life span, mechanisms of removal, phagocytosis, and other physiologic functions Despite the large number of studies bearing on these and related problems, it must be admitted that large gaps in knowledge exist where, in reality, very little is known about the actual functions, activities, and destiny of the leukocytes It is the purpose of this review to evaluate the literature bearing on the leukocyte and leukopathic disorders since approximately January of 1953

Physiology and Metabolism

The desoxyribonucleic acid content of normal and leukemic human leukocytes has been estimated microspectrophotometrically with the Feulgen dye [Petrakis (1)] The average DNA[2] control of normal lymphocytes was twice that of normal spermatids In acute and chronic lymphocytic leukemia, lymphocytes with contents above the expected diploid value were frequently encountered, suggesting that cells with active mitotic activity are released into the circulation in the leukemias In studies on leukocyte phosphorus partition, Bardawill and co-workers (2) found that DNA turnover measured with P^{32} was most rapid in acute leukemia and very slow in chronic lymphocytic leukemia The lowest values for acid soluble and phospholipid phosphorus were found in chronic lymphocytic leukemia The metabolism of sulfur as measured by L-cystine and sodium sulfate incorporation also varies in normal and leukemic leukocytes [Weisberger *et al* (3)] L-cystine is readily incorporated by both, but incorporation is most rapid by the cells of acute leukemia In contrast only the leukocytes of chronic granulocytic leukemia incorporate sodium sulfate rapidly

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[1] The survey of literature pertaining to this review was concluded in July, 1954.

[2] The following abbreviations were used in this chapter: ACTH (corticotropin), DNA (desoxyribonucleic acid), TEM (triethylene melamine).

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eral investigations Intact leukocytes and leukocyte homogenates fortified with co-factors of the glycolytic and respiratory enzyme cycles actively consume oxygen, utilize glucose, and produce lactic acid [Beck & Valentine (4); McKinney *et al.* (5)]. A primarily aerobic glycolytic metabolism appears to be present with a glycolytic-respiratory ratio of as high as 30 to 1 being observed in cells from normal subjects and subjects with chronic myelocytic leukemia, and 15 to 1 in those from subjects with chronic lymphocytic leukemia [Beck & Valentine (6)] The leukocytes of both chronic myelocytic and lymphocytic leukemia exhibit greatly reduced glycolytic and respiratory capacities as compared to normal cells. Efforts to determine a rate-limiting defect in glycolysis in leukemia have shown that both the triose phosphate dehydrogenase and lactic dehydrogenase enzymes are reduced in amount about proportional to the observed reduction in glycolytic rate in leukemic leukocytes, while the pyridine nucleotide co-factors of glycolysis appear to be present in about a normal amount [Beck & Valentine (7)]. However, the activities of these enzymes still exceed the observed over-all glycolytic rate, and their reduction cannot be considered as causative of the reduced glycolysis Anaerobic glycolysis is initiated in leukocytes by the initial phosphorylation of glucose to glucose-6-phosphate by means of the adenosinetriphosphate dependent hexokinase reaction Free glucose inhibits glycogen breakdown which occurs in the presence of adenylic acid derived as a result of adenylpyrophosphatase activity of the cells [Wagner & Yourke (8)]. In diabetes mellitus intact leukocytes produce more lactic acid from fructose than glucose while the reverse is true in leukocytes of normal subjects [Martin *et al* (9)]. Glucose utilization by leukocytes in vitro is increased by insulin in subjects with diabetes but not in normal subjects Cortisone and hydrocortisone in vitro in concentrations of 0 1 to 1 0 μg per ml cause diminution in lactic acid production by leukocytes, and it has been suggested that this might be related *in vivo* to a slow and abnormal evolution of the inflammatory reaction [Martin *et al* (10)].

Granulocytic leukocytes contain glycogen in substantial amounts This is normal in uncontrolled diabetes and in subjects receiving ACTH[2] and cortisone, is increased on a per cell basis in neutrophilic leukocytosis and in many cases of polycythemia vera with leukocytosis and leukemoid features, and is substantially reduced on the average in chronic granulocytic leukemia [Valentine *et al* (11)]. Studies on leukocyte glucuronic acid indicate that substantial amounts are present in cells from normal blood, that leukemic blast cells and lymphocytes are very poor in this constituent, and that the lymphocytes in benign lymphocytosis, such as infectious mononucleosis, also contain little glucuronic acid [Follette *et al* (12)] By inference it appears likel [illegible]

gree [illegible]
(14)] Compared to normal values, unit leukocyte alkaline phosphatase is very high in most neutrophilic leukocytoses and in polycythemia vera with

leukemoid features and very low in chronic granulocytic leukemia. These metabolic differences are not dependent upon or explained by morphologic differences in the cell populations analysed, for morphologically identical populations show very marked and consistent differences in different disease states. In man, but not in all animal species, marked elevations in unit leukocyte alkaline phosphatase occur over a 72 hr. period with administration of large doses of purified ACTH gel, though the relationship of this phenomenon to pituitary-adrenal function has not been defined The wide and sometimes consistent variations in morphologically identical leukocyte populations in disease promises to be of value in differentiating chronic granulocytic leukemia and myeloproliferative syndromes and leukemoid reactions closely resembling leukemia morphologically.

The studies by Riley (15, 16) on tissue mast cells suggest that these cells are probably an important repository of histamine as well as heparin. Intravenous histamine liberators produced disruption of tissue mast cells, a phenomenon prevented by premedication with antihistaminics (15). Ehrich (17) has postulated that the well-known marked elevation of leukocyte histamine in granulocytic leukemia correlates with the increased numbers of basophils in this condition Unpublished observations on leukemic blood containing very high percentages of basophils in the author's laboratory strongly suggest that this is the case. It has also been reported that a material having the biological and physical properties of heparin has been extracted from acetone-dried leukocytes of a patient with mast cell leukemia [Martin & Roka (18)] These observations suggest a close relationship of the blood basophil and the tissue mast cell, which possess in common the characteristic metachromatically staining granulation In human subjects, cortisone has been found to reduce the absolute basophil count as well as the eosinophils, and, at the same time, blood histamine is always decreased [Code & Mitchell (19)] It has again been pointed out that the elevations of blood histamine in chronic granulocytic leukemia cannot be entirely abolished by therapeutic measures or clinical remissions, a fact which now can be probably correlated with the persistence of increased number of basophils even in remissions of the disease [Kelemen *et al* (20)] Since histamine metabolism shows important variations from species to species, it can not be inferred that the apparent prominent relationship of the basophil to blood histamine in man applies to all species

It is becoming increasingly apparent that while the eosinopenia following ACTH administration reliably reflects adrenocortical activation, the eosinopenia of nonspecific stress requires interpretation of factors other than the adrenal cortex [Laidlaw & Jenkins (21), Thorn (22)] Injection of epinephrine, for example, produces eosinopenia but without proportionate increase in oxysteroids of blood or urine or in ketosteroid excretion, and there is no evidence that epinephrine eosinopenia is attributable to ACTH release. Since in stress both ACTH release and epinephrine release may occur, stress eosinopenia may include non-adrenocortical contributing factors with epinephrine

as a prototype (22). The mechanism of glucocorticoid induced eosinopenia has also been the subject of several investigations (23 to 26). In one study by Root and co-workers (26) on bone marrow changes associated with the immediate eosinopenic response to ACTH, there was no evidence of disturbed eosinophil maturation nor of depletion of mature eosinophils by rapid removal or destruction. It appears probable that these agents do not prevent marrow eosinophilopoiesis, do not have direct lytic effects, and do not result in distributional shifts in the vascular or tissue compartments or cause fixation at the site of physiologic demand It has been postulated that the eosinopenia may be attributable to (*a*) increased destruction by the R-E system and (*b*) inhibition of eosinophil release from marrow. Blocking of the R-E system has been found experimentally to prevent glucocorticoid eosinopenia [Esselier *et al.* (23)]. Vaughn (27) has postulated that the chief function of the eosinophil in man is to transport histamine or histamine-like material from bone marrow to the tissues for inactivation This does not appear to the author to correlate well with recent evidence in man on the basophil as a repository of blood histamine, nor with the dubious relationship of blood histamine levels and eosinophilia in human subjects.

Several reports are available on the leukocytic response to epinephrine (28 to 31). The usual reaction is leukocytosis which occurs independently of the presence of the spleen (28, 30, 31). On the basis of studies on the time relationships of granulocytosis appearing in peripheral arterial and portal vein blood after injection of epinephrine into the splenic artery, it has been concluded that the immediate increase in leukocytes is attributable to release from the pulmonary circulation and possibly later release from the portal organs Studies on the epinephrine test have not substantiated its diagnostic specificity in hypersplenic cytopenias [Chatterjea *et al.* (28); Groissier & Ruberman (31)] A syndrome closely mimicking hypersplenism and correctible by splenectomy has been produced experimentally by intraperitoneal injection of methyl cellulose [Palmer *et al* (32)].

The vexing problem of definitive elucidation of leukocyte utilization, life span, and turnover has continued to receive attention Three groups of investigators (33, 34, 35), employing measurement of P^{32} labeled DNA turnover as a criterion, have found this to be very slow in the lymphocytes of chronic lymphocytic leukemia and postulate a "life span" of one to several months for lymphocytes in the disease By similar techniques the "life span" of the granulocytes has been estimated as a matter of a few days In other studies employing leukocyte infusion and cross transfusion in man, leukocyte production was estimated at 1.3 to 59 6 million per min , and the life span of the polymorphonuclear granulocyte to be 96 hr and the lymphocyte 56 hr. [Bierman *et al* (36)] Since there are objections to all techniques thus far employed, it appears likely that definitive settlement of this problem has not yet been made In measurements of leukocyte intravascular survival using quinacrine (Atabrine) tagged leukocytes collected in ACD solution, tagged cells were found for 30 to 90 min. in normal subjects and somewhat

longer in leukemic recipients [White (37)]. The subtle changes occurring rapidly in leukocytes withdrawn into anticoagulants, labeled, and reinjected make for severe interpretive difficulties in relating experimental results to *in vivo* events

Miscellaneous metabolic or physiologic alterations in leukocytes have been reported in a variety of experimental situations Frank & Dougherty (38) have reported that under conditions of stress lymphocytes morphologically identical to Type II Downey cells appear in the peripheral blood and may be produced by a nonadrenocortical mediated response. Sequestration of leukocytes in peripheral capillaries has been found to accompany intraarterial injection of histamine [Bierman *et al* (39)] In animals, differences in chemotaxis of leukocytes occurred with differences in nutrition, the leukocytes of fasting animals being attracted to a wider variety of saccharides than those of normal animals. The possibility of glycogen being a natural granulocyte-attracting agent released on tissue injury has been discussed [Kuna & Chambers (40)] Neither ACTH nor cortisone in therapeutic doses was found by Moeschlin and co-workers (41) to influence phagocytosis of *Staphylococcus aureus* by white blood cells.

Leukemia and Lymphoma

Frequency, distribution, mortality—The incidence of leukemia and lymphoma has been the subject of several investigations (42 to 46) In a comparison of frequency, distribution, and mortality at the University of California Hospital from 1913 to 1947, Shimkin and co-workers (42) found that duration of life in chronic lymphocytic leukemia averaged 42 months and in acute lymphocytic leukemia 5 4 months Prognosis as regards survival was not significantly greater between 1940 to 1947 than in the 1930 to 1940 period Survival in the lymphosarcomatous group varied depending on the type of involvement Over-all five year survival was 24 per cent, but was only 2 per cent in patients with initial visceral involvement, considerably higher in the primarily lymphadenopathic group, and 46 per cent in giant follicular lymphoma [Shimkin *et al* (46)] The relationships of the various forms of lymphoma to each other and to leukemia have been discussed by Berman (47). A working classification of neoplastic lesions of lymph nodes suggested is the division into reticulum cell type, lymphoblastic type, lymphocytic type, and mixed type The latter includes Hodgkin's disease where the cytologic picture is pleomorphic and shades in Hodgkin's sarcoma into the picture of the reticulum cell type, and giant follicular lymphoma where lymphoblastic, lymphocytic, and reticulum cell features may be represented in the proliferative process

Etiology—The etiology of leukemia still remains an unsolved problem and it is quite possible that multiple etiologies or precipitating factors will be found Dameshek (48), in a recent review, has suggested that myelotoxic agents such as x-rays and chemicals and viruses are among the most probable of various possibilities, and that hereditary predisposition may play an im-

portant role. Evidence supporting the virus hypothesis has been advanced by Gross (49 to 54), based on (*a*) the greater frequency of leukemia in certain kinships in chickens, mice, cattle, and man and (*b*) direct experimental evidence in chickens and mice. It is suggested that a group of submicroscopic, cell-free, oncogenic agents exist, which, like egg-borne virus diseases, are transmitted "vertically" through the embryo. Usually, according to this hypothesis, these agents are dormant, but are occasionally activated by obscure means and produce clinical leukemia. The number of individuals with leukemia, then, would represent only a small fraction of those carrying the "seeds" of the disease. Continued observations by Lange *et al.* (55) on the atomic bomb survivors in Hiroshima and Nagasaki indicate that there is a great increase in leukemia in the heavily exposed groups, that this is equally manifest in both sexes and at all age levels, that chronic lymphocytic leukemia has been uncommon (though chronic lymphocytic leukemia is also comparatively rare in unexposed Japanese), and that cases are still appearing in the exposed group, though declining in number since 1950. The development of lymphoma in a strain of mice with high spontaneous incidence has been observed to be inhibited by administration of cortisone, while a high incidence of granulocytic leukemia appeared in a low leukemia strain of mice irradiated once with 350 r [Upton & Furth (56)] Cortisone was without effect on the induction of granulocytic leukemia. The leukemogenic effects of single, acute doses of substantial amounts of whole body irradiation appears well established.

Clinical and metabolic features.—The protean clinical features of leukemia are well known, but unusual clinical manifestations are deserving of some comment. The association of pregnancy and leukemia has been again reported and the literature reviewed [Shub *et al* (57)] In view of frequent reports of acute exacerbations and death during pregnancy or in the first eight months post partum, it is suggested that pregnancy may have deleterious effects in this disease. In view of the fact that many cases normally terminate with this acute picture, careful statistical analysis would be necessary before a valid conclusion can be reached, however Interesting temporary remissions in acute leukemia occur at times during a variety of infectious processes, and 11 additional cases in children have been reported and discussed [Bierman *et al.* (58)]. In these cases, the usual course of events was onset of fever, reduction in peripheral leukocyte count, occasionally the development of

disease are reversible Sleisenger and co-workers (59) have called attention to association of the sprue syndrome with lymphoma of the small bowel and the suggestion made that lymphoma of the small bowel deserves consideration in the differential diagnosis of this syndrome A case of sickle cell anemia terminating with acute myeloblastic leukemia has been reported (60), though the coexistence of the two conditions is presumably fortuitous. Lame

and co-workers (61), in a study of malignant lymphomas of the gastrointestinal tract, found that lymphomas constituted 20 per cent of all malignant tumors of the stomach, nearly half those of the small bowel, while the colon was uncommonly involved. Case reports have also appeared on the association of cyclic neutropenia with giant follicular lymphoblastoma and lymphosarcoma (62), on the coexistence of chronic lymphocytic leukemia and polycythemia vera (63), on polycythemia terminating as acute myeloblastic leukemia (64), and on the development of acute granulocytic leukemia in a patient with reticulum cell lymphoma (65).

Metabolic investigations in granulocytic leukemia have demonstrated the presence of abnormal ultraviolet absorbing nucleic acid derivatives in urine [Horrigan (66)] In three cases, these were identified as the pyrimidine uracil. In two other cases, the abnormal metabolite requires further characterization. Studies on antibody formation in various types of leukemia by Larson & Tomlinson (67), have shown frequent severe impairment in chronic lymphocytic leukemias, and usually normal values in other leukemias and lymphomata studied, unless the patient was receiving cortisone medication. In the latter situation, impairment was noted (67) Patients with active leukemic and lymphomatous diseases store nitrogen and phosphorus readily and more phosphorus than normal. Transfer of nitrogen from host to tumor occurs when diet is inadequate to meet needs of both, and, with regression induced by therapy, there is some evidence the released nitrogen may be used in replenishing host tissue [Fenninger *et al* (68)] Elevated bone marrow pressures have been found by direct measurement in leukemias (69). After therapeutic splenic irradiation in granulocytic leukemia there is a decrease in mitoses in marrow myeloid cells within 80 min This is followed by a decrease in immature myeloid elements, an increase in immature erythroid elements, or both [Gunz (70)] In leukemic subjects receiving radioactive As^{76}, Block and co-workers (71) found insufficient evidence of cytolysis to account for observed remissions, and no evidence that the immature dividing cells were more sensitive to irradiation by the As^{76}.

Therapy.—Recent years have seen the experimental and clinical trial of large numbers of potential therapeutic agents A few, while never curative, have shown promise as useful adjuncts in the therapy of leukemia and lymphoma This review will discuss chiefly the newer chemotherapeutic agents rather than x-irradiation and radioactive phosphorus (P^{32}) Nitrogen mustard, triethylene melamine (TEM), urethane, folic acid antagonists, and indeed all of the known chemotherapeutic agents of value have marked limitations in prolonging life, but have made important contributions to patient comfort and productivity and to the research of chemotherapy of these disorders [Gellhorn (72)] Skipper (73) has called attention to the possible common pattern of action of many of these agents through interference with nucleotide metabolism. It should be emphasized, however, that in most instances mechanism of action is still poorly understood in definitive terms.

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five cases of acute monocytic leukemia by intramuscular injection of fresh glandular fever serum proved ineffective (89). Phenylbutazone (Butazolidin) has been suggested as having some symptomatic benefit in controlling pain, fever, anorexia, and in some instances pruritis in Hodgkin's Disease (90).

Certain syndromes involving leukemoid blood reactions, proliferative disorders of marrow or extramedullary hematopoiesis or both may closely mimic granulocytic leukemia at times (91 to 95). These include myelofibrosis, some cases of polycythemia vera (94), and a heterogeneous group of myeloproliferative disorders to which a highly varied terminology has been applied in the medical literature. It has been postulated but not proved that these have in common a neoplastic or proliferative process involving primitive mesenchymal cells (93, 95), that splenic enlargement is not compensatory for marrow failure but part of the fundamental proliferative process, and that extramedullary collections of cells are autochthonous formations and not infiltrates [Hutt *et al* (93)]. Peace (95) has also postulated that "myelonecrosis" may be the initial histopathologic lesion, followed by compensatory proliferation, poorer cell differentiation, and sometimes fibroblastic or osteoblastic proliferation. Extramedullary hematopoiesis by this concept is an expression of the latent capabilities of the primitive mesenchymal cell system. The exact inter-relationships of these syndromes are not clear, however, and it is quite possible that they represent a superficially similar response to a heterogeneous group of metabolic defects or stimuli.

Multiple myeloma represents a proliferative disorder involving the plasma cell, similar fundamentally to leukemic and lymphomatous proliferation involving other leukocyte types. Schwartz & Cataldo (96) have reviewed clinical and laboratory aspects in detail. In metabolic balance studies, conducted by Adams *et al* (97) on patients with myeloma receiving ACTH, serum and urine proteins decreased, and in two of these subjects the major reduction in the elevated serum protein was attributable to reduction in the abnormal globulin present. In one patient a good clinical remission lasting two years was obtained, though myelomatous involvement of the marrow continued to be evident during remission. Studies have been reported both on the abnormal serum proteins (98) and the Bence-Jones urinary protein in this disorder (99). In ten cases of myeloma, three with palpable spleens, splenic aspiration showed increased numbers of plasma cells in nine (100). An unusual case simulating hyperparathyroidism has also been the subject of a detailed clinical and pathologic study (101).

Other Leukopathies

A number of studies have appeared on various aspects of infectious mononucleosis. Involvement of the heart in this disease has been discussed in detail with the conclusion that while myocarditis accompanies this disease, there is no reason to believe chronic heart disease occurs in those who recover [Houck (102)]. While a number of reports of cardiac changes have been reported, the evidence adds up to an unimpressive total, and minor electro-

the nitrogen mustards in the treatment of leukemia and lymphoma (74 to 83). TEM[2] has hemopoietic toxic effects similar to nitrogen mustard, but can be given orally, intramuscularly, or intravenously and usually with minimal nausea. Reports agree that remissions may be obtained in some patients with Hodgkin's disease (74 to 81), though in some hands (74) therapeutic benefits have not been as gratifying as reported elsewhere. Opinion varies as to efficacy in other lymphomatous disorders, poor results being reported in lymphosarcoma and reticulum cell sarcoma (74, 79), as well as evidence of some clinical and hematologic benefit in certain cases (77). Some degree of benefit has been noted in cases of chronic lymphocytic leukemia (77, 79) Dosage schedules vary widely and have been discussed in detail [Bond *et al.* (74); Axelrod *et al* (79)]. The dangerous and toxic effects of marrow aplasia have been emphasized [Wilkinson *et al.* (75)]. It is the opinion of the author that TEM has its chief advantage in that the oral route of administration is available, that the indications for its use are very similar to those of nitrogen mustard, and that toxic and therapeutic effects are both somewhat less predictable than with nitrogen mustard therapy. A series of ethylene-imine derivatives (triethylenephosphoramide, or TEPA, diethylene phosphoramide or DEPA and triethylene thiophosphoramide or Thio-TEPA) have been demonstrated as also possessing nitrogen mustard-like activity (78, 82, 83) They appear to add little range to the therapeutic armamentarium, but, unlike nitrogen mustard, can be given intramuscularly.

Myleran (1,4-dimethanesulfonyloxybutane), a sulfonic acid ester with alkylating properties, has proved to have definite depressive effects on the myeloid leukocytes of man and animals and to be of benefit in the management of chronic granulocytic leukemias [Petrakis *et al* (84); Galton (85); Haddow & Timmis (86)] It is given orally There is no effect in acute leukemias or in chronic leukemias other than the chronic granulocytic variety. The early results indicate that it may become a useful adjunct in the chronic granulocytic leukemias.

A new antimetabolite 6-mercaptopurine, a purine analogue, also shows some promise. Good temporary remissions occur in about one-third of children with acute leukemia, in occasional adults with acute leukemia, and in some cases of chronic granulocytic leukemia both early and late in the disease [Burchenal *et al* (87)]. The lymphomas in general respond poorly The drug is effective at times when folic acid antagonists and ACTH or cortisone have become ineffective In general, therapeutic resistance develops more rapidly than to folic acid antagonists. The distinct advantage exists that, unlike folic acid antagonists, toxic side effects other than excessive marrow depression are comparatively minimal

Other agents of dubious or less established value have been also employed in the hope of obtaining symptomatic relief or clinical remissions in these disorders. The production of pyridoxine deficiency with its antimetabolite desoxypyridoxine produced a very brief clinical remission in one of four cases of acute lymphocytic leukemia (88) Attempts to obtain clinical remission in

blood, the L-E phenomenon by this hypothesis being assumed to be an antigen-antibody reaction involving autoantibodies [Dittrich & Fruhmann (118)]. In other experiments, artificial L-E cells could be produced by normal serum heated to 58°C. with a high molecular weight polyvinyl-alcohol-polysulfuric acid ester [Inderbitzin (119)] The suggestion was made that the L-E cell may depend upon abnormal mucopolysaccharides combined with gamma globulins In still another investigation, an inhibitor of desoxyribonuclease (DNAse) and of the L-E phenomenon were found and had many properties in common. Proof of identity requires further purification, but the authors postulate that the serum L-E factor may act by deranging an intracellular DNAse-DNAse inhibitor system. The depolymerization of DNA which characterizes the L-E phenomenon would, by this concept, be secondary to this derangement [Kurnick *et al.* (120)]. Incubation of L-E serum with the leukocytes of various animal species reveals marked species differences (121). L-E cells have been observed in smears of untreated, freshly drawn peripheral blood in a moribund patient, suggesting that this is truly an *in vivo* as well as *in vitro* phenomenon (122) The nature of the phenomenon cannot be regarded as elucidated as yet The leukopenia of paroxysmal nocturnal hemoglobinuria may be due to premature leukocyte destruction by the same factors that result in erythrocyte hemolysis and thrombocytopenia Occasionally, aregenerative crises occur which may result in agranulocytosis, severe anemia, or both [Crosby (123)] The leukopenia resulting from nitrogen mustard (HN_2) administration can be mitigated by L-cysteine and considerably less effectively by D-cysteine administered a short time before the medication. Studies indicate that this effect depends on spatial configuration as well as on the close apposition of SH, NH_2, and COOH groups of the molecule. It seems that the protective effect of L-cysteine may not be entirely due to chemical inactivation of HN_2 *in vivo* [Weisberger & Storaasli (124)] It should be emphasized that these experimental observations do not imply that L-cysteine should be given clinically in conjunction with HN_2, or that therapeutic effectiveness can be safely predicted if this were done.

Cytology

The findings on lymph node imprints in normal, hyperplastic, and lymphomatous tissues have been discussed in detail by Moore & Reagan (125). These have proved to be a useful adjunct to tissue studies Thoracic duct lymph, studied by direct cannulation of the duct in living human subjects, was found to contain 210 to 5600 leukocytes per mm in nonleukemic subjects In lymphocytic leukemic blood, the leukocyte count usually did not exceed that of peripheral blood [Bierman *et al.* (126)] Erythrocytes were few in number in nonleukemic lymph, but present up to 1.5 million/c. mm. in the lymph of leukemic patients Refractive neutral red staining particles are present in some lymphocytes of normal blood and are said to be increased in persons receiving whole body irradiation or toxic chemicals of certain types.

cardiographic deviations may overconcern doctor and patient (102) Hepatitis is perhaps of more concern. Attempts to influence the clinical course of infectious mononucleosis with antibiotic therapy were unsuccessful in 78 cases [Walker (103)]. The occasional occurrence of the Guillain-Barré syndrome in this disease has been discussed with case presentations [Raftery *et al.* (104)], as has been the occurrence of acute pericarditis (105), thrombocytopenic hemorrhagic diathesis (106, 107), and immune body acute hemolytic anemia (108)

Osgood (109) has presented an extensive review of drug-induced agranulocytosis and hypoplastic anemia. The mechanism and treatment of these disorders is discussed. Among the drugs listed as high risk agents producing granulocytopenia are aminopyrine, nitrophenols, thiouracils, and thiosemicarbasones Low risk agents which have been incriminated include antihistaminics, phenothiazines, and procaine amide hydrochloride (109) Case reports of severe agranulocytosis attributable to phenylbutazone (110, 111) and 4-amino-antipyrine (111) have been added to the literature. Considerable interest has been manifest in the possible immunologic etiology of certain agranulocytic or granulocytopenic syndromes (112 to 115). In one unusual patient reported (113), persistent neutropenia accompanied a pathological serum globulin constituting 30 per cent of the total serum protein, and this globulin fraction was capable of agglutinating normal leukocytes in dilutions of 1 to 120. While not definitely proved, this may have been the causative agent of the patient's neutropenia. In one study, sera of about 2,000 normal subjects and 600 patients with various diseases were tested for leukoagglutinating properties by a relatively simple test employing defibrinated blood [Dausset *et al* (115)] In 19 subjects positive reactions were obtained, and in 18 of these, leukopenia with neutropenia was the sole clinical feature common to all. In such sera, the leukoagglutinating property was confined to the globulins and serologic and physicochemical properties were considered to favor its being an antibody. It is suggested that certain categories of leukopenias may be on the basis of autoantibodies against leukocytes, and hence analogous to acquired hemolytic anemias with autoantibodies Antileukocytic serum has been prepared experimentally (114) and was capable of producing marked clumping of granulocytes and leukophagocytosis resulting in inclusions often indistinguishable from L-E cells The same report reviews the literature on antileukocytic sera

Numerous investigations of the L-E cell phenomenon have been reported The methodology of the L-E test and the clinical interpretation of this and related phenomena has been reviewed by Dubois (116) The L-E phenomenon has been demonstrated by Walsh & Zimmerman (117) in severe penicillin hypersensitivity reactions, suggesting that it may be related to other hypersensitivity reactions as well as to systemic lupus erythematosus Experimentally, it has been suggested that phagocytosis of homologous cells is influenced by changes on the surface of cells and by an opsonic factor acting in

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These have been studied in terms of refractive index, solubilities, and staining reactions [Hempelmann & Knowlton (127)]. They are considered as possibly lipid or phospholipid in character and may be related to the Golgi apparatus. In a study by Klein & Block (128) of bone marrow plasmacytosis in 60 cases, the degree of plasma cell proliferation was correlated with the clinical diagnosis and the plasma globulins Elevation of plasma globulins of some degree was present in 80 per cent. The diseases most frequently associated with marrow plasmacytosis were myeloma, rheumatoid arthritis, Hodgkin's disease, granulomatous, and collagen diseases. Plasmacytosis in the hemopoietic organs of dogs exposed to x-irradiation has also been observed (129). Using the phagocytosis of colloidal gold intravenously administered and of formolized *Staphylococcus albus* administered intraperitoneally in mice as a criterion of macrophage activity, no interference could be demonstrated after cortisone administration [Gell & Hinde (130)]. In the rabbit peritoneal cavity, monocytes were no less subject to chemotaxis than granulocytes, and their advance toward a chemotactic object even more direct [Harris (131)]. In a study of the Pelger-Huet familial leukocyte anomaly in a Japanese family, genetic data supported a simple Mendelian type of inheritance (132). The cytology of the degenerating leukocyte has been discussed (133). A method permitting the separation and to some extent preservation of leukocytes with details on preservation media has been presented [Tullis (134)]. The author discusses the meaning of "viability" tests including Brownian movement, amoeboid activity, ability to resist socalled "impermeable" dyes, and phagocytosis While some progress has undoubtedly been made in the right direction, satisfactory preservation of leukocytes cannot be regarded as a solved problem.

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NUTRITION AND NUTRITIONAL DISEASE

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We have entered a new era of nutrition which has altered our approach to experimental and clinical problems We owe much to the biochemist, microbiologist, endocrinologist, and geneticist for laying the groundwork. The essential events of nutrition go on in the living cell, which must be presented with a balanced diet that may or may not resemble the diet presented to the total animal The essential nutrients act in large part as components of cellular enzyme systems. Superimposed upon these enzyme systems are hormones which seem to exert regulating effects on enzyme reactions.

Transfer of food from environment to cell is a major problem in nutrition. There are at least three aspects to this problem

(*a*) The transfer of food from the environment to the gastrointestinal tract The ingestion of food is a very complicated process involving interactions between the nervous system and many physiologic processes. Many mechanisms are involved in the control of food intake, and their study is rendered difficult by intermingling of psychologic and physiologic factors which must be separated for proper experimental approach

(*b*) Digestion comprises processes by which food as found in the environment is transformed into compounds that can be utilized by the cells Enzymes must digest food without digesting the gastrointestinal tract The gastrointestinal tract synthesizes enzymes and produces hormones that regulate digestive secretions Dominating all these activities are the nervous and endocrine systems through which the environment plays a role The microbiological flora also may play a significant role in nutrition

(*c*) After the food is processed, it must be absorbed and, before delivery to the cell, most nutrients pass through the liver Liver metabolism is partly dependent on the pancreas, and is greatly influenced by other endocrine glands and the state of the circulation

Many nutritional studies are hard to interpret because of difficulties in establishing adequate controls. The whole question of what type of control is needed is a vexing one That pair feeding results in dissimilar weights is expected from known impairment of food utilization in many deficiency states Pairing animals to similar weights may more nearly approximate a "true control," but, depending upon what phenomena are being studied, it might be appropriate to pair them to similar body fat content, body protein content, body water content, or other measurable entities

For example, in 1939 it was observed that pantothenic acid deficient rats had severe changes in the adrenal cortex, consisting of varying degrees of hypertrophy, degeneration, and hemorrhage. These were not found in controls on *ad libitum* food intake. There were additional difficulties in interpreting the observed results which arose because some degree of infection was found in all the animals exhibiting gross adrenal defects, although in many the infection was well-concealed, being found only on careful examination of the middle ears (1).

The intervention of "non-specific stress" and depletion including starvation and infection may greatly alter function and structure. Complex interrelationships between various nutrients add further difficulties to the problem of assessing and interpreting nutritional investigations.

Food Intake and Obesity

Obesity is reputedly the most serious nutritional disorder in the United States (2) It is seen as a link between nutrition and many degenerative diseases (3, 4) The possible dangers of obesity have been abundantly stated, but a lack of unanimity is seen in reports of better prognosis of obese patients with coronary disease (5), in myocardial infarction (6), and reportedly in studies in hypertension in Denmark (7).

Obesity results from abnormal function of mechanisms regulating appetite and satiety on the one hand, and caloric expenditure on the other; and a breakdown of any one of many mechanisms could result in defective regulation These mechanisms, psychological and physiological, are so intermingled that separation for critical experimental attack is difficult with available techniques. The questions may be stated thus. Is simple overfeeding, resulting from habit or emotional disturbance, the basis of obesity, or are there abnormal metabolic processes, genetic or acquired, which impair satiety mechanisms or hinder delivery of stored fat for energy conversions, in a program of weight reduction should caloric intake be markedly restricted, or is it possible, without semi-starvation, to activate physiological forces which encourage utilization of depot fat? Long experience has shown that severe caloric restriction, semistarvation, is intolerable except where motivation is so strong as to overshadow severe symptoms

Obesity as "Compensatory Hypertrophy of Adipose Tissue."—It has been proposed by Pennington (8 to 12) that the metabolic defect of obesity is the diversion, during digestion and absorption, of an abnormal amount of the caloric intake to the adipose tissue, and inhibition of the mobilization of fat from the adipose tissue in the post-absorptive state, denying to the cells energy needed to carry on their normal metabolic processes The resulting under-nutrition of these cells is reflected as "hunger" In effect, adipose tissues parasitize the rest of the body.

In this view, the altered metabolism is caused by decreased ability of the obese animal to oxidize pyruvic acid which accumulates in excessive quanti-

ties In the human the only evidence for this consisted of elevation of blood lactic acid in the obese (13, 14). Pyruvic acid is the precursor of lactic acid. Abnormal elevation of blood pyruvic acid in the diabetic after mild exercise is not prevented by insulin (15), suggesting a common denominator between obesity and diabetes in impaired oxidation of pyruvic acid. Diabetes results only after an additional abnormality in carbohydrate metabolism from insulin insufficiency ensues (9). Excessive accumulation of pyruvic acid has been found in hereditarily obese mice (16).

Assertedly, excessive pyruvate inhibits conversion of fatty acids to ketone bodies, oxidation of fatty acids by the tissues (17), and oxidation of acetate (16, 18) Thus, pyruvate not only inhibits utilization of fat for energy, but also interferes with oxidation of acetate, so that this important intermediate in both carbohydrate and fat metabolism, instead of serving as a source of energy, is diverted to the depots to be deposited as fat. The resulting cellular under-nutrition activates homeostatic mechanisms regulating food intake and the animal experiences hunger.

This vicious cycle, the "dynamic phase of obesity," when energy intake exceeds expenditure, continues until the "static phase of obesity" is reached when energy intake and expenditure are balanced and weight gain ceases. With this "compensatory hypertrophy of the adipose tissue," even with only partial utilization of fat, enough is made available to supply the energy needs of the body during the post-absorptive state (8). The mass of fat needed to accomplish this differs in different individuals and probably depends upon the degree of metabolic impairment. The ingestion of more food is needed to meet the energy needs of active tissue cells because it is not available from adipose tissue where it is stored.

Obese people subjected to calorically restricted diets, therefore, are forced into a state of under-nutrition with consequent hunger, reduction of work output, and total metabolic rate Their limited caloric intake has an exaggerated capacity to meet their low caloric needs, frequently necessitating unbelievably low caloric intake if weight increases are to be avoided. Obese mice also show very marked reduction in basal metabolism (19) and in activity (20)

According to Pennington, the ingestion of a low sodium ketogenic diet makes weight reduction possible with relatively high caloric intake The ketogenic diet appears to increase total metabolic rate and mobilization and oxidation of fat from adipose tissue. The very low intake of carbohydrate prevents the accumulation of pyruvic acid, thus decreasing the latter's inhibitory effects on fat utilization. A ketogenic diet causes ketonemia with increased mobilization of fat from adipose tissue (21), elevation of blood fatty acids resulting in acceleration of oxidation (22), and increased utilization of fat (23).

Evidence for the effectiveness of such diets in treating obesity by Pennington is impressive Whether such diets will be sufficiently palatable over

long periods of time remains to be seen. That such diets are possible over very long periods of time is known, since Eskimos live on a ketogenic diet. However, when they have access to the high carbohydrate diet of white men, they prefer it.

Sodium restriction experimentally decreases the efficiency of food utilization largely by increasing total metabolism (24). How much sodium restriction in the human is necessary to accomplish this remains to be seen, but an experimental basis for this certainly exists.

Glucostatic Theory of Food Intake and the Meaning of A-V Blood Glucose Differences.—Mayer and his group (2, 16, 19, 20, 25 to 28) have associated hunger and satiety with variations in arteriovenous blood sugar differences, such that in human subjects satiety is associated with differences of 15 mg per 100 cc. or more, and appetite or hunger is associated with differences approaching 0 mgs. per 100 cc This was confirmed by other work showing that arteriovenous glucose differences of 20 mg per 100 cc was associated with abolition of gastric contractions and subjective experience of hunger. Decrease of the difference toward 0 was associated with return of gastric contractions and subjective hunger (29).

A-v blood glucose differences return to low levels in obese subjects sooner than in non-obese, suggesting that increased utilization of carbohydrate is associated with obesity (30) Increased utilization of carbohydrate could be interpreted to mean increased lipogenesis, the absorbed carbohydrate being diverted to adipose tissue at abnormally rapid rates Difficulty in mobilization of stored fat must be assumed to account for the obesity in this hypothesis. As yet, similar studies with different types of diets have not been reported It may be that only on diets of particular types will there be this close correlation between appetite, satiety, and alterations in a-v blood glucose differences

Appetite and satiety—Understanding the basic physiology of appetite and satiety would improve the approaches to the problems of obesity This is well-appreciated by many investigators and there are currently three lines of investigation aimed at better understanding of these mechanisms They all deal with the absorption and disposal of nutrients and how these processes affect the hypothalamic satiety (31) and feeding centers (32) Brobeck (33) postulates that food intake is controlled by temperature regulation, such that increase in total body heat initiates impulses inhibiting feeding mechanisms. Decrease in body temperature causes the animal to become active, searching for food and ready to eat (34) Incompatibilities with other observations (27) may be explainable by differences in comparing normal rats with rats with hypothalamic injury

Kennedy (35, 36) regards adipose tissue as a major factor in regulating food intake Feeding behavior of obese animals is different from non-obese Dietary dilution with inert materials such as kaolin resulted in normal non-obese rats increasing food intake so that caloric intake and body weight re-

mained unaltered, whereas rats rendered obese by hypothalamic injury did not maintain caloric intake and lost weight. These findings are similar to those reported in mice rendered obese by injection of gold thioglucose (37).

Lundbaek & Stevenson (38) found that normal rats and hypothalamic-injured, obese rats maintained caloric intake when changed from high carbohydrate to high fat diets, but reduced caloric intake when changed from high fat to high carbohydrate diet. The obese animals however reduced food intake much more than the normal It was concluded that the obese state in itself is a determinant of the capacity of the carbohydrate disposal mechanisms.

These various lines of investigation suggest that satiety is associated with active disposal of nutrients from the blood; the hypothalamus is the center where changes in internal chemistry, caused by disposal of the nutrients absorbed during digestion, are translated, through the nervous system, into expressions of appetite and satiety; the most important process of disposal involves lipogenesis, the synthesized fat being stored largely in the adipose tissue In the post-absorptive period the organism draws upon stored fat for energy, which means the fat is very labile in character. That adipose tissue is metabolically very active has been shown by several lines of study (39). On the basis of nitrogen content adipose tissue is as active in lipogenesis as the liver (40). Phosphorylase content of adipose tissue in obese women was three times as high as in normal women, and, after reduction of weight to normal, the phosphorylase content of their adipose tissue returned to normal (41). The important role of adipose tissue in appetite and satiety suggests that further work be done along the lines suggested by Hoelzel that hydration and dehydration of adipose tissue exert important effects upon appetite and satiety (42).

Hormonal control of disposal mechanisms—After a meal, glucose is readily oxidized or synthesized into glycogen and fat and these reactions are facilitated by insulin (43) In the post-absorptive state utilization of glucose is inhibited by the pituitary, largely via growth hormone (44) With glucose unavailable as a source of energy, fat mobilized from depots supplies needed energy The mobilization of fat is also under pituitary control with growth hormone as the active agent It requires the "permissive" action of adrenocortical hormones (45)

Thyroxin was found to inhibit the action of the fat mobilizing factor of the anterior pituitary in an interesting study in guinea pigs (46) which is difficult to interpret It does raise the interesting clinical question as to whether thyroid hormone in the absence of hypothyroidism may not be self-defeating.

Diet and Obesity—The type of diet ingested plays a role in food intake, but its action is obscure Low protein diet decreased food intake in humans (47), but not in all cases Various inhibitors which are normally occurring constituents of food decrease food intake, and the subjection of foods to various processing procedures influences food intake in animals, depending upon

the food and the processing methods employed (48). Foods also may carry compounds which evoke appetite or satiety and these factors are perhaps responsible for the differences in the continuing acceptability of foodstuffs Food flavors and spices deserve more investigation.

Treatment with Calorically Restricted Diets.—Treatment of human obesity with low calorie diets is based upon the assumption that obesity is never directly caused by abnormal metabolism but by food habits that are not adjusted to metabolic requirements (49). Obese individuals after losing weight on low calorie diets maintained a constant weight only on food intake considerably lower than that of other individuals of similar age and dimensions, suggesting the existence of a metabolic difference such that the formerly obese person must subsist on a low calorie diet the rest of his life if he chooses to control his weight by this means (12). This difference is due in part to decreased total caloric output which is itself part of the obesity defect. Observations have shown that obese subjects on a reducing diet experience a decrease in basal caloric output whereas normal individuals who have put on excessive weight by forced overeating experience no such decline in basal metabolic output (10)

THE GASTROINTESTINAL TRACT

Immunity of the living gastrointestinal tract to autodigestion involves protective mechanisms not yet well-defined. The concept of a "two-component self-generating mucous barrier" (50) helps give direction to studies of biochemical and cellular components. The non-vital layer of viscous material, the normal mucus, shields the surface epithelium from digestive en- [illegible]

may be ascribed to the relative physical impenetrability of the mucus layer and to its ability to adsorb enzymes and acid

As the second line of defense, the columnar and cuboidal cells of the surface and crypts regenerate with remarkable rapidity, replacing continuously cells injured and shed Ulceration may result from disturbance or loss of these barriers

Although most such work refers to the upper gastrointestinal tract, similar phenomena involving the colon are known (51) Such studies have been concerned largely with influences of the nervous system and hormones Malnutrition may also be modified by these factors

Reinterpretation of existing experimental information upon the relation between intestinal function, ulceration, and nutritional deficiencies is needed. Diets deficient in vitamin A (52), thiamine, pantothenic acid or calcium (53, 54), B complex vitamins (55), thiamine (56), riboflavin and inanition (57), protein (58, 59, 60), and vitamin E (61) affect the enzyme systems and tis-

sues, possibly in proportion to the metabolic activities of the various tissues and may result in ulceration.

Rats with tocopherol deficiency did not develop ulcers when also deficient in vitamin A, pyridoxine, or essential unsaturated fatty acids. Administration of any one missing nutrient without tocopherol resulted in increased food intake and ulcers occurred, a "stress of realimentation" (61). Concurrent administration of vitamin E prevented ulceration.

Pantothenic acid deficient rats, as well as rats maintained on low food intake, had a marked decrease in the respiratory activity of the intestinal mucosa. The respiration of the mucosa was raised significantly by diets containing 60 per cent protein. The pantothenic acid deficient rats had severe abnormalities of intestinal mucosa consisting of atrophy and scattered hemorrhages not found in the controls on reduced food intake (63). The authors (Vitale *et al.*) concluded that the defects resulted specifically from pantothenic acid deficiency, but the data show that the semi-starved control animals reached weights twice as high as the deficient The authors discussed the difficulties inherent in adequate control groups

Severe atrophy of intestinal mucosa is also found in starvation. In a comprehensive study of human starvation and semi-starvation of subjects confined to concentration camps during World War II, Danish workers (64) found extensive changes in the whole gastrointestinal tract, over and above what could be ascribed to specific vitamin or other deficiencies. They studied fasting rats and found that as early as the fourth day there were atrophic changes of the mucosa of all segments of the small intestine, coupled with decreased resistance of the superficial layers to trauma or irritants.

Undernutrition results in loss of protein from the gastrointestinal mucosa. These losses represent not just stored protein, but functional material such as enzymes upon which the functional activity as well as the structural integrity of the gastrointestinal mucosa depends (63, 64).

That the intestinal mucosa has powers to adapt its enzymes to the nature of the food is shown by the hexokinase content of the small intestine of rats chronically fed different diets The lowest hexokinase activity was found in the mucosa of rats fed a high fat diet and the highest activity in those fed a high carbohydrate, fat-free diet (65).

Effect of Intestinal Bacteria and the Role of Antibiotics—The preponderance of *Lactobacillus bifidus* in the intestinal flora of the human nursling prompted a search for microbiological growth factors in human milk. A strain of *Lactobacillus bifidus* requiring an unknown growth factor was isolated The concentration of this factor is high in human milk and low in cow's milk, and it is also present in hog gastric mucin It seems to be a mucin, containing galactose and acetylglucosamine. *In vitro*, acid hydrolysis destroys its activity (66, 67).

The effects of such mucins may be to encourage a more benevolent gastro-

intestinal flora that produces less toxins or is less destructive of compounds beneficial to the host. Intestinal bacteria may be beneficial to the host, synthesizing essential nutrients present in the diet in inadequate amounts (68).

Because of the high concentration of both microorganisms and vitamins in the cecal contents, it had been assumed that vitamins were synthesized in the cecum by the flora. However, in germ-free chicks the cecal vitamin content closely approximates that of conventional chicks (69). The germ-free chicks grow as well as normal chicks. Germ-free guinea pigs, on the other hand, die on diets that support good growth in conventional animals Despite voracious appetites and high food intake, they die of starvation, presumably because of inadequate digestion of foods which, in guinea pigs, requires the activity of microorganisms (69).

The rabbit, though a non-ruminant, may be classed with the ruminants because it utilizes nutrients synthesized by intestinal bacteria, by ingesting a special type of night feces, consumed as soon as voided. They closely resemble cecal contents rich in protein, microorganisms and vitamins (70). The enzyme systems of the intestinal flora may be considered as part of the enzyme systems of the total animal.

Increasing prominence is being given to the destruction of nutrients by intestinal bacteria. Such studies are made possible by the availability of antibiotics, and by the use of germ-free animals reared in environments in which no microflora exists. The addition of certain antibiotics in small amount to the diet increases the rate of growth and efficiency of food utilization of many kinds of animals These effects are not obtained in environments in which bacteria or other infective agents are absent, such as in the chick embryo or in germ-free animals. Antibiotic-sensitive bacteria capable of interfering with food utilization inhabit the intestinal tracts of many animals. Suppression of these bacteria may be responsible for a decreased destruction of nutrients, rendering them available to the hosts for increased growth and efficiency of food utilization (71, 72).

The remarkable relation of wheat (or rye) even in very small amount to celiac disease in children and non-tropical sprue or idiopathic steatorrhea in adults (73) is attributed to the gluten fraction, particularly the gliadin. The mechanism is unknown. These diseases respond incompletely or not at all to folic acid and vitamin B_{12} In contrast, tropical sprue is related closely to the ingestion of unsaturated fats, which easily undergo oxidative rancidity, with formation of peroxides and polymers, and folic acid, liver extract, and vitamin B_{12} are very effective (74). Sprue-like syndromes (without anemia) frequently observed as untoward reactions to chlortetracycline and oxytetracycline (75) are relieved, frequently dramatically, by oral folic acid. Discontinuation of folic acid may result in relapse, with relief on retreatment (76). The treatment may have to be continued for months The development of these syndromes in individuals on good diets, within a few days of starting oral antibiotics, does not suggest deficiency disease caused by loss of vita-

mins synthesized by intestinal microorganisms, nor is there evidence that yeasts are causally related. The possibility exists that the chelating properties of the drugs induce biochemical change in enzyme systems in the intestinal mucosa

THE LIVER

The liver is interrelated in a mutually protective manner with other organs such as the pancreas which has been referred to as the "guardian" of the liver (77). This protective action comprises the insulin mechanism which prevents migration of depot fat to the liver and is necessary for synthesis of glycogen; and its external secretions needed for digestion of dietary protein, which protects the liver against injury

The liver standing in a "protective manner" between the environment and other body tissues may detoxify noxious agents in the food or produced in the intestine, since these reach the liver immediately after absorption.

Toxins and Detoxification —The term detoxification has teleological implications, assuming that metabolism of poisons follows special pathways, and proceeds in the direction of the formation of less toxic compounds This assumption is unwarranted because of lack of information concerning relative toxicity of the parent substances and their derivatives The transformations of "toxic compounds" as well as the nutrients of food stuffs, depend upon the enzyme systems with which the animal is endowed (78, 79, 80). Enzyme systems may be affected variously. A nutritional deficiency may deprive an enzyme system of an essential component A conditioned nutritional deficiency may be brought about by excessive destruction or excretion of an essential nutrient The protein moiety of an enzyme system may be inactivated by the blocking of an essential structure such as functional —SH groups The general connotation of "toxin" would fit this last category.

Different species have different assortments of enzyme systems Rats possess an enzyme that methylates nicotinamide, and are depleted of methionine which furnishes methyl groups for the obligatory methylation of nicotinamide before excretion Nicotinamide is thereby "toxic" to rats Guinea pigs and rabbits, not possessing the necessary methylating enzyme systems, do not methylate nicotinamide for excretion and large doses of nicotinamide are innocuous to them (81) Different species show different types of injury when fed similar abnormal diets On diets low in protein and lipotropic compounds the dog, rat, mouse, rabbit, hamster, calf, pig, and duckling developed fatty livers, which are difficult to produce in guinea pigs. Diets low in lipotropic compounds produce severe kidney lesions in rats, and to a lesser degree in young pigs and calves, whereas young mice and puppies, both of which develop fatty livers, do not develop kidney lesions (82).

A possible role of the gastrointestinal microflora has already been discussed Hepatoxins, whether produced in the gut or present in the diet, are carried to the liver by the portal circulation and may interfere with enzyme

systems by action upon the protein moiety, the coenzyme, or the mineral component.

Experimental Liver Disease Produced by Dietary Means.—In liver disease resulting from abnormalities of diet, as in other nutritional disorders, progress rests upon reproducing the disease in experimental animals Two distinct types of liver injury have been produced by dietary means: hepatic necrosis, characterized by hemorrhages and massive cell death, and cirrhosis, usually preceded by fatty infiltration (83).

Hepatic necrosis, produced by various types of diets, is cured or prevented by the sulfur containing amino acids, Vitamin E, or factor 3, an unidentified factor associated with casein (84). Experimental observations of liver damage produced by dietary means were confused and difficult to interpret because both types of injury occurred together. This resulted from the nature of the diets used: low in protein, high in fat, and low in lipotropic compounds. The nutritional factors which have been shown to play a role in liver necrosis and cirrhosis are shown in Table I (85, 86).

TABLE I

NUTRITIONAL FACTORS IN LIVER NECROSIS AND CIRRHOSIS

Nutritional Factors	Liver Necrosis	Liver cirrhosis
Protein	beneficial	beneficial
Methionine	beneficial	beneficial
Cystine	beneficial	injurious
Vitamin E	beneficial	no effect
Choline	no effect or injurious	beneficial
Dietary fat	no effect or injurious	injurious
Vitamin B_{12}	no effect or injurious	beneficial
Folic acid, citrovorum factor	no effect or injurious	beneficial
Betaine	no effect or injurious	beneficial
Factor 3	beneficial	unknown
Methyl group precursors	no effect or injurious	beneficial

Hepatic Necrosis—Liver damage is caused not only by cystine deficiency but also by cystine excess *It was with an excess of cystine that liver injury* was first produced by dietary means (87) Cystine may be the substrate of an enzyme reaction which fails if cystine is absent and fails if it is in excess It is a "well-known feature of many enzyme systems that they are inhibited by a surplus of the substrate" (88)

A conditioned deficiency of cystine is produced by the hepatoxin, bromobenzene, which combines with cysteine, is acetylated, and excreted as mer-

capturic acid (89, 90). Presumably the bromobenzene drains off cystine and its precursor, methionine, so that in effect liver necrosis results from deficiency of sulfur amino acids rather than from direct cell toxicity. Cystine and methionine protect against bromobenzene; vitamin E or methylene blue showed no protective action (91); liver damage was aggravated by fasting (92).

The chemical structure of the halogenated hydrocarbon has a decisive bearing upon its toxicity. Mercapturic acid is formed by the conjugation of bromobenzene with cysteine in the para position. If the para position is occupied by another halogen, the dihalogenated compound has little toxicity, whereas if the second halogen is in the meta position, this dihalogenated compound produces liver damage—because the para position is still free to combine with cysteine (91)

Cystine utilization is blocked by a metabolic inhibitor, present in selenized wheat. Selenium in the wheat protein replaces the sulfur of cystine, producing the selenium analogue, which competes with cystine in liver metabolism and produces liver necrosis when fed to rats (93). Protein is protective (94).

Intestinal bacteria seem to play a role in liver necrosis That the large intestine might be a site of hepatoxin formation was supported by studies showing that pathologic changes in the livers of rats on yeast-containing necrogenic diets occurred predominantly in the left half, which received portal blood chiefly from stomach, spleen, and large intestine. Portal blood to the right half of the liver comes chiefly from the small intestine (95). It was *postulated that the sulfur amino acids and vitamin E absorbed from the* small intestine protected the right half of the liver, whereas bacterial toxins from the large intestine produced necrosis. Chlortetracycline (aureomycin) added to the necrogenic diet was temporarily effective in preventing necrosis because of establishment of chlortetracycline-resistant strains, whereas the protection afforded by vitamin E or cystine was permanent (85)

The evidence was open to two interpretations antibiotics, by inactivating intestinal bacteria, might have prevented the synthesis of toxins, or they could have prevented the destruction of essential nutrients such as vitamin E or the sulfur amino acids This was clarified by studies with germ-free rats fed necrogenic diets (96) When fed *ad libitum*, germ-free rats did not develop liver necrosis, but conventional rats fed the same diet did. This lent credence to the concept of intestinal intoxication However, the investigators noted that the germ-free animals consumed more food than the controls. When food intake of germ-free rats was restricted to that of the controls, they, too, developed liver necrosis (96) Here the level of food intake became a decisive factor in the development of liver injury. It is tempting to conclude that the increased food intake raised the intake of sulfur amino acids to protective levels

The present position is that no conclusive evidence has been obtained

that a positive factor arising from intestinal activity is essential to the production of dietary hepatic necrosis. Intestinal bacteria may, however, play a role by changing the food intake of the animal or by destruction of sulfur amino acids or other essential nutrients.

Uncertainty as to whether cystine alone is the protective factor or methionine also, arises from the interchangeability of cystine and methionine. Since methionine can be converted to cystine, feeding methionine is equivalent to feeding an unknown mixture of the two. Cystine cannot be converted to methionine. This dilemma was resolved by diets in which the sole source of protein was a mixture of pure amino acids. When ample cystine was available, methionine deficiency led to macrocytic anemia and hypoproteinemia, but not to hepatic necrosis Omitting cystine and giving methionine just sufficient to prevent anemia and hypoproteinemia caused typical massive necrosis (95, 97) Thus methionine may play a triple role in liver function: it may supply cystine; it may act as a lipotropic factor to prevent fatty liver and cirrhosis, and it may act to maintain normal formation of erythrocytes and plasma proteins

The sulfur amino acids may vary extraordinarily in liver protein metabolism The N:S ratio of liver protein of pups and of normal adult dogs is 11 or 12 to 1 The protein-depleted dog which is so sensitive to liver injury shows a N:S ratio of 14 or 15 to 1 When protein-depleted dogs are fed adequate amounts of methionine or of cystine, they are incorporated into liver protein so that the N:S ratio of the liver becomes 8 4 when methionine is fed and 11 3 when cystine is fed, implying that liver proteins have a variable makeup in a dynamic system (98)

Vitamin E and Massive Liver Necrosis—Understanding the mechanisms by which vitamin E protects the liver would greatly facilitate an understanding of hepatic necrosis In general, vitamin E has the following actions: prevents muscular dystrophy (99), prevents vascular disturbances including exudative diathesis and encephalomalacia (100, 101), prevents pigmentation of tissue (ceroid formation) (102), prevents nerve degeneration (103); and acts as an antioxidant *in vivo* and *in vitro* (104).

The nerve and muscle degeneration are obscure beyond their histological descriptions The vascular disturbances and the pigment formation seem to be related to the antioxidant property of vitamin E.

The exudative diathesis and encephalomalacia of chicks, as well as the brown coloration of adipose tissue in rats and chicks, are produced by diets deficient in vitamin E and containing highly unsaturated, easily oxidizable, fatty acids (105) The fatty acids undergo oxidation *in vivo* with the appearance in the adipose tissue of peroxides followed by brown discoloration It has been postulated that the oxidation of fatty acids involves, early in the process, the formation of a free radical which produces the damage to the capillaries, causing hemorrhages and exudation (105)

Presumably, the oxidation of unsaturated fatty acids *in vivo* occurs in

the presence of hematin compounds, and studies *in vitro* have shown a catalytic action of cytochrome C, hemin, hemoglobin, and catalase (106). Studies *in vitro* of the compounds occurring in animal tissues that catalyze the oxidation of unsaturated fatty acids showed that they were all inhibited by vitamin E as well as by other well-known antioxidants, showing the reaction to be non-specific (107). During the oxidation of unsaturated fatty acids *in vitro*, hemoglobin and hemin are destroyed (108). Neither porphyrins nor bile pigment derivatives were found as cleavage products, indicating that the hemin is split into smaller molecules. Apparently, the destruction of hemin is coupled with the auto-oxidation of unsaturated fatty acids. It is of the greatest significance from the standpoint of the total animal that only linoleic and linolenic acids are able to destroy any appreciable amount of hemin, and they are precisely the unsaturated fatty acids that undergo *in vivo* auto-oxidation (108).

Information on the role of vitamin E as an antioxidant has come from studies of the hepatoxins carbon tetrachloride (109), pyridine (110), tri-o-cresyl phosphate, and chlorinated naphthalene. While they all differ somewhat in their action, they have in common the property of producing liver necrosis which can be prevented or ameliorated by vitamin E or high levels of protein. All are pro-oxidants, accelerating the development of rancidity in fats *in vitro* All data obtained are consistent with the hypothesis that these compounds exert toxic biological effects through pro-oxidant activity in unsaturated lipid systems (111). They may act by destroying tocopherol *in vivo* during the oxidative process Studies of tissue slices show an increased rate of respiration in vitamin E deficient animals (112) and animals injected with CCl_4 (113) Vitamin E administered to the animal restored the respiratory rates to normal Carbon tetrachloride given to young rats on vitamin E deficient diets containing 10 per cent casein decreased the ability of liver slices to synthesize creatine from guanidoacetic acid and methionine The same changes were noted to a lesser degree in vitamin E deficient rats not given carbon tetrachloride, indicating that carbon tetrachloride acted by aggravating the vitamin E deficiency (114, 115)

Tocopherol protects red cells against hemolysis by dialuric acid, and this has been attributed to its antioxidant action (116) It increases the utilization of protein (117) It increases the survival time of rats and guinea pigs subjected to anoxia (118). Excess dietary fat decreases survival time of anoxic rats The role of tocopherol in anoxia assumes greater significance in the light of the part played by anoxia in massive liver necrosis (95) The liver cell is sensitive to low oxygen tension, which renders it more subject to necrosis Thyroxin, which increases the demand for oxygen, increases the severity of the lesions due to chloroform. Carbon tetrachloride greatly increases the liver lesions of animals exposed to low oxygen tensions The oxygen supply to the liver lobule is an important factor in the production and localization of the necrosis due to chlorinated hydrocarbons There are two possible ex-

planations for this: either oxygen is necessary for detoxification, or the necrosis is the result, not of cytotoxic action, but of deprivation of oxygen. Such deprivation might result from ischemia, and there is experimental evidence that exposure to the chlorinated hydrocarbons is followed by marked restriction of the intralobular circulation (95).

Chlorinated hydrocarbons may impair intracellular oxygen availability in another way. Their pro-oxidant action may accelerate the removal of oxygen from liver cells by accelerating oxidation of highly unsaturated fatty acids present in the liver. These are present in greater concentration in the liver than in extrahepatic tissues, because of the high phospholipid content of the liver. Phospholipids have such an avidity for highly unsaturated fatty acids that they virtually fractionate ingested dietary fats, selectively incorporating the highly unsaturated fatty acids into their molecules. Small amounts of dietary fats may greatly increase the iodine number of phospholipids without affecting the iodine number of the neutral fat Cod liver oil is outstanding among the various fats in its ability to increase the level of unsaturation of the tissue phospholipids (119). It is precisely cod liver oil which, when fed at high dietary levels, induces the greatest amount of liver damage, presumably by precipitating a vitamin E deficiency Through its antioxidant activity, vitamin E conserves the oxygen supply of the liver cell

Liver Necrosis and Enzyme Systems.—For a proper understanding of the interchangeability of such chemically different compounds as cystine and vitamin E in protecting against liver damage, it will be necessary to understand fully the common denominator through which these compounds act.

Factor 3 deficiency induces liver necrosis In such deficient animals a consistent defect of respiration was found in liver but not in kidney or diaphragm Long before histologic hepatic lesions appeared, oxygen consumption of liver slices fell to 50 per cent or less of the initially normal rate. Antinecrogenic factors such as vitamin E, cystine, or factor 3 prevented the specific respiratory defect (120)

Necrotic rat liver showed a defect in the oxidation of pyruvate A marked lowering of coenzyme A was found, and both vitamin E and the sulfur amino acids tended to preserve the coenzyme A levels (121) The lowering of the coenzyme A content of the livers preceded the onset of necrosis, accompanied by decrease in both pyruvate oxidation and lipogenesis Cystine sulfur seems to be incorporated into coenzyme A "It is probable that vitamin E which prevents both hepatic necrosis and, to a large extent, the changes in coenzyme A content in these animals, is involved in the sulfur amino acid metabolism leading to coenzyme A synthesis" (122)

It seems that cystine functions as a substrate and the role of vitamin E is catalytic Four hundred to 800 molecules of cystine are required to produce as much liver protection as one molecule of vitamin E (84)

It has been suspected that reversible oxidation-reduction reactions are involved in the functioning of both cystine and vitamin E since both of them participate in such reactions Vitamin E does this through its ability to de-

velop a free radical, the semiquinone radical (123), and cystine, by virtue of its —SH group. The concept that cystine and vitamin E exert protective effects as components of reversible oxidation-reduction systems is fortified by studies with methylene blue, a reversible oxidation-reduction indicator, which also prevents hepatic necrosis and lung hemorrhage in rats fed low protein, vitamin E deficient diets (124). Methylene blue also resembles vitamin E in increasing storage of vitamin A (125), stimulating growth of vitamin E deficient chicks (126), protecting rats injected with pyridine against liver damage (110), and preventing peroxidation of adipose tissue (127). It has been suggested that a function of vitamin E is "to prevent spontaneous oxidation in a living vessel filled with easily oxidizable substances, surrounded and permeated by a reactive atmosphere" (128).

Fatty Liver and Cirrhosis.—Most experimental production of fatty livers and cirrhosis is complicated by some degree of hepatic necrosis, largely because of the use of very low protein diets. Rats fed excess nicotinamide, producing uncomplicated deficiency of lipotropic agents, developed fatty liver and an inhibition of growth Restoration of growth required methionine, while betaine, choline, cystine, and homocystine were ineffective Choline plus homocystine restored growth via synthesis of methionine (81).

Fatty livers caused by ethionine (a methionine antagonist) were prevented by methionine, but choline was ineffective. Glucose in large doses prevented or cured the fatty changes but failed to prevent death, indicating that methionine served in some capacity in addition to its lipotropic effect. Ethionine produced fatty livers in females and castrates, but not in males Testosterone protected both females and castrated males against fatty infiltration, possibly because of its protein-sparing properties (129).

Fatty livers are produced by choline deficiency. When choline deficient diets are also low in protein, liver damage may coexist. Large amounts of choline will remove large parts of the excess lipids without influencing the liver damage (130) Vitamin B_{12}, and to a lesser extent folic acid, protects the liver in choline deficiency by sparing choline (131). The lipotropic effect of vitamin B_{12} may be related to its stimulation of methionine formation which has been shown to occur *in vitro* from choline and homocystine (132).

Possible Choline and Vitamin E relationships—There is evidence that choline is functionally related to vitamin E Muscular dystrophy accompanied by fatty and cirrhotic livers has been produced in choline-deficient rabbits on diets adequate in vitamin E. Creatine excretion increased, as in vitamin E deficiency Addition of choline immediately decreased creatinuria Choline-deficient rats with cirrhotic livers absorb vitamin E very poorly, as shown by low plasma levels of vitamin E Doses of vitamin E massive enough to raise plasma levels to normal did not prevent muscular dystrophy, ruling out vitamin E deficiency as a factor (133) Perhaps the question should be raised as to whether a choline-deficient cirrhotic liver can metabolize vitamin E normally.

Additional evidence for some sort of interrelationship between choline,

planations for this: either oxygen is necessary for detoxification, or the necrosis is the result, not of cytotoxic action, but of deprivation of oxygen Such deprivation might result from ischemia, and there is experimental evidence that exposure to the chlorinated hydrocarbons is followed by marked restriction of the intralobular circulation (95).

Chlorinated hydrocarbons may impair intracellular oxygen availability in another way. Their pro-oxidant action may accelerate the removal of oxygen from liver cells by accelerating oxidation of highly unsaturated fatty acids present in the liver. These are present in greater concentration in the liver than in extrahepatic tissues, because of the high phospholipid content of the liver. Phospholipids have such an avidity for highly unsaturated fatty acids that they virtually fractionate ingested dietary fats, selectively incorporating the highly unsaturated fatty acids into their molecules. Small amounts of dietary fats may greatly increase the iodine number of phospholipids without affecting the iodine number of the neutral fat. Cod liver oil is outstanding among the various fats in its ability to increase the level of unsaturation of the tissue phospholipids (119). It is precisely cod liver oil which, when fed at high dietary levels, induces the greatest amount of liver damage, presumably by precipitating a vitamin E deficiency. Through its antioxidant activity, vitamin E conserves the oxygen supply of the liver cell.

Liver Necrosis and Enzyme Systems.—For a proper understanding of the interchangeability of such chemically different compounds as cystine and vitamin E in protecting against liver damage, it will be necessary to understand fully the common denominator through which these compounds act.

Factor 3 deficiency induces liver necrosis. In such deficient animals a consistent defect of respiration was found in liver but not in kidney or diaphragm. Long before histologic hepatic lesions appeared, oxygen consumption of liver slices fell to 50 per cent or less of the initially normal rate Antinecrogenic factors such as vitamin E, cystine, or factor 3 prevented the specific respiratory defect (120)

Necrotic rat liver showed a defect in the oxidation of pyruvate A marked lowering of coenzyme A was found, and both vitamin E and the sulfur amino acids tended to preserve the coenzyme A levels (121) The lowering of the coenzyme A content of the livers preceded the onset of necrosis, accompanied by decrease in both pyruvate oxidation and lipogenesis Cystine sulfur seems to be incorporated into coenzyme A "It is probable that vitamin E which prevents both hepatic necrosis and, to a large extent, the changes in coenzyme A content in these animals, is involved in the sulfur amino acid metabolism leading to coenzyme A synthesis" (122)

It seems that cystine functions as a substrate and the role of vitamin E is catalytic. Four hundred to 800 molecules of cystine are required to produce as much liver protection as one molecule of vitamin E (84)

It has been suspected that reversible oxidation-reduction reactions are involved in the functioning of both cystine and vitamin E since both of them participate in such reactions. Vitamin E does this through its ability to de-

Many questions are raised by the "protective" effect of low levels of nutrition as shown by these histologically normal livers Are these livers "normal"? Fasting may not be very different from the undernutrition imposed upon these animals, and fasting animals are more subject to liver injury by the chlorinated hydrocarbons than are well-fed animals. Would these undernourished animals be more sensitive than well-fed animals to toxins or infections?

The separate components of a necrogenic diet were investigated to secure more information on the meaning of the protective effect of undernutrition upon the liver. Feeding 3.5 grams daily of a yeast-containing necrogenic diet fully protected the rats against liver necrosis. On the same diet on *ad libitum* food intake the rats died of liver necrosis "The increased consumption of sucrose, salt mixture and Torula yeast protein was without any effect, whereas that of lard precipitated death from liver necrosis within 2 days" (143). Here it appears that the protective effect of undernutrition is the result of a decrease in the intake of lard to such low levels that it does not exert its toxic action. Under other conditions fatty livers were produced by raising the caloric intake, and increasing the proportion of sucrose to protein. Supplementation with sucrose resulted in liver damage which was preventable by protein or choline (149)

Low environmental temperatures decreased liver necrosis while the greatest incidence of liver injury occurred in the region of "thermoneutrality." In this temperature range the liver is responsible for a large part of the metabolic activity. At lower environmental temperatures or in undernutrition other tissues play a larger part. An attempt should be made in studying liver injury to evaluate the relative metabolic rates of the liver and the rest of the body (139)

Age of the animal plays a role in liver injury Rats weaned on necrogenic diets at 17 days had a higher incidence of liver disease than those weaned at 25 days (139) After 35 days of age there was marked decrease in choline requirement in rats (142).

Proteins, Amino Acids and the Liver.—No single factor plays a more consistent role than protein in protecting the liver Increased dietary protein through its content of cystine and methionine protects against fatty liver, cirrhosis, and necrosis, but proteins exert physiological effects beyond those of these amino acids. The quality of the protein as determined by its pattern of amino acid distribution is important (150, 151) Diets containing maize as the source of protein resulted in fatty livers prevented by choline or methionine

On low protein diets choline prevents fatty liver but has little effect upon cell damage (130) Cell damage with high liver fat is accompanied by decreased phospholipid Choline relieves the fatty infiltration but does not restore the ability of liver slices to synthesize phospholipids There seems to be no simple relationship between the two processes The lowered rate of phospholipid synthesis is probably directly related to decrease in liver protein,

vitamin E, and liver damage comes from work on ceroid. This golden-yellow pigment first observed in the cirrhotic livers of choline-deficient rats (83) was also found in the livers of rats on diets low in vitamin E and lipotropic agents, and containing highly unsaturated lipids—suggesting that the pigment is formed from unsaturated lipids by auto-oxidation. Vitamin E or methylene blue decreased the amount of hepatic ceroid (134, 135). A similar pigment in the uteri of vitamin E-deficient rats gave the same characteristic histochemical reactions as oxidized cod liver oil (136), showing a direct relationship of highly unsaturated dietary fats to their oxidation products in the tissues, and demonstrating *in vivo* oxidation of unsaturated fatty acids. The tissue pigment has been shown not to result from ingestion and absorption of preformed products of highly oxidized, unsaturated, fatty acids (105).

Under some conditions, vitamin B_{12} aggravates the liver necrosis of vitamin E deficiency The livers of B_{12}-deficient chicks contained about five times as much coenzyme A as normal controls (137) It is noteworthy that vitamin B_{12} may act in an antagonistic capacity to vitamin E, both in the production of liver necrosis and in its effect on hepatic coenzyme A Whereas vitamin E deficiency causes a decrease in hepatic coenzyme A, B_{12} deficiency increases it greatly (121, 122, 137).

Guinea pigs do not develop fatty livers on low choline diets, presumably because their livers do not contain choline oxidase Rats on similar rations develop fatty livers because their livers presumably contain choline oxidase which destroys the very choline these livers need Nickel, a choline oxidase inhibitor, prevents fatty liver in rats on choline-deficient rations (138).

Restriction of Food Intake and Liver Damage.—Food intake plays a decisive role in liver injury Restriction of food intake alone produces little liver damage (139 to 143) Inadequate attention to food intake as a factor arising from experimental conditions may lead to a misinterpretation of results Thyroidectomy, thiouracil, and propylthiouracil protected against liver injury, which suggested that the thyroid was involved in maintaining the integrity of the liver Thyroidectomy, however, decreases food consumption; normal rats pair-fed with thyroidectomized rats are also protected against liver necrosis, showing that the restriction of food intake as well as the loss of thyroid hormone can confer protection (140, 144, 145) Estrogens protect the liver and females showed less severe hepatic lesions than males on cirrhosis-producing, low choline diets (146, 147) Implantation of diethylstilbesterol pellets in castrate male rats lowered food intake and retarded growth (148). Animals with retarded growth resulting from decreased food intake have less histologic evidence of fatty liver Rats on a 20 per cent casein diet have high levels of food intake and normal livers As dietary nicotinamide is increased, there is decrease in food intake and progressive increase in liver fat up to a maximum, after which further decreases in food intake lead to decrease in liver fat, until normal liver fat content is attained at the point where growth ceases (81) The role of food intake in such studies as well as in all endocrinological studies needs to be carefully considered.

lator even when examined A specific volley of nerve impulses or an isolatable extract are possible links in the chain or elements in a complex. Repeatedly it is found that many factors vary simultaneously, each one as central as any other, and only by convenience of thought is one exalted above another.

Whether the existing body of knowledge of experimental liver disease can be useful in prevention and cure of human liver disease depends upon similarities between human beings and experimental animals in reactions to nutrients known to play roles in protecting the liver Basically, the human being answers to the same biochemical laws as do other living systems. Depending on the pattern of his enzyme systems the human being may present certain differences in reactions to metabolites, but these are by no means beyond our biochemical powers to investigate In clinical liver disease degeneration already may have occurred, perhaps having been chronic for some time. The liver may have been injured by known or unknown environmental or dietary toxins or infection. Establishing the role of dietary factors in such situations may be difficult or impossible. However, a survey of available evidence indicates that when rats and humans are put on the same low protein diets, low in lipotropic factors, liver abnormalities are produced In both, the abnormalities were prevented or repaired by supplementation with protein The rats developed fatty livers and the humans developed clinical evidence of liver injury with enlargment of the liver, abnormal retention of bromsulphalein, and abnormally high blood levels of lactic and pyruvic acids after oral administration of glucose (165). In Western countries human beings rarely subsist on diets comparable in deficiency to those required for the production of experimental liver injury in animals Massive liver necrosis among human populations occurring purely as a result of malnutrition is unknown. It is difficult to assemble a diet of natural foodstuffs, acceptable as food, which is so deficient as to cause massive necrosis For the production of liver necrosis in humans the cooperation of a positive factor, such as an infective agent or a toxin, for example, chlorinated hydrocarbons, would seem to be required There may be increasing possibility of attainment of this situation with the progressively increased use of processed food and the increased application of chlorinated hydrocarbons to crops in pest control operations.

Cirrhosis of the liver is common in human populations in the African and oriental tropics where it is clearly associated with low protein diets similar to those which produce cirrhosis in animals. That environmental temperatures are involved is an interesting speculation, in view of the work in animals (139). Liver disease constitutes a large part of Kwashiorkor, "the most serious and widespread nutritional disorder known to medical and nutritional science " Kwashiorkor has been dealt with elsewhere in detail (166, 167). The child develops the disease rapidly when weaned directly on to an adult diet low in protein, very low in fat, and very high in carbohydrate (force fed by the mother) (168). These are precisely the experimental conditions in which rats weaned directly upon a low protein diet develop liver damage. The chil-

which is reflected in lower levels of enzyme systems in the liver accounting, in part, for the altered phospholipid synthesis (152). These results with the total animal have been confirmed *in vitro*. Liver slices from rats on low protein diets synthesized phospholipids at lower rates than controls Adding choline to the low protein diet prevented or reversed fatty infiltration but did not increase the ability of liver slices to synthesize phospholipids (152) Similar results were obtained with dogs (153).

Fatty liver, cirrhosis, and liver carcinoma are associated in rats chronically deficient in choline Similar results were obtained with chickens Supplementation with choline or vitamin B_{12} prevented these abnormalities (154). Riboflavin in very large doses also prevented tumor development (155). Monkeys with protracted deficiency of pyridoxine, which is closely associated with amino acid metabolism, developed not only fatty livers but also severe nodular cirrhosis (156).

On diets low in casein both methionine and cystine increase growth and the regeneration of liver protein (157). On low casein diets unsupplemented with nicotinic acid, cystine depresses growth. When nicotinic acid, tryptophane, or fat is added, cystine will stimulate growth (158).

An excess of methionine of only two to three times the optimum depresses growth and food intake Body tissue protein is lost while at the same time there is an increase in liver protein and plasma globulin (159). On the other hand, excess choline does not lead to unusual physiological effects (159).

The growth-depressing effects of excess methionine was counteracted by high levels of protein (160) Glycocyamine protected chicks (161) but not rats (162). Excess methionine was completely counteracted by a combination of molar equivalents of glycine and arginine plus vitamin E, folacin, and vitamin B_{12} Dietary vitamin E and methionine, on the other hand, counteracted the growth-depressing effect of glycine excess (162)

Implications of Experimental Liver Disease on Liver Disease in the Human Being

Knowledge of human nutritional disorders is much less advanced than that of such disorders in experimental animals How much human liver disease is induced nutritionally and what might be done with nutritional therapy cannot be clearly decided as long as we do not know all the dietary factors needed to protect the liver nor the interrelationships between them. Liver disease, a worldwide problem, is possibly the most important dietary disease of mankind today (163), but "the constellation of factors governing the integrity of the liver is now so great that any claim made for . . a particular factor in safeguarding the liver can have only a limited application" (150). The observations of Adolph in 1943 (164) in connection with water metabolism is also pertinent here.

The theory that a single governing factor exists for a physiological activity does not appear now to be substantiated Moreover, there is no means of recognizing a regu-

coupled with the production of cirrhosis by dietary means without alcohol led to the current concept that the chronic ingestion of alcohol leads to, or is associated with, a specific type of dietary deficiency which results in fatty infiltration of the liver, and that cirrhosis is the direct result of such infiltration (174) Excessive alcohol could be deleterious because the full load of its metabolic disposal is thrown upon the liver. It is suggested that the incidence of liver injury is higher when the liver bears a disproportionately large share of the metabolic load (139).

The craving for alcohol has been investigated on the supposition that the excessive ingestion of alcohol arises from nutritional or metabolic difficulties (177) Rats subjected to deficiencies of various water soluble vitamins increased their intake of alcohol, and decreased it when the nutritional deficiency was corrected Other studies (178, 179) indicated a more complex relationship It was of great interest that the voluntary intake of alcohol was increased by rats with cirrhotic livers induced by carbon tetrachloride, and that the increased alcohol intake was seen as the consequence of the cirrhosis and not of the pharmacological action of the carbon tetrachloride (180)

> . . the facts . . induce us to believe that voluntary alcohol intake is increased when a difficulty in the utilization of energy of carbohydrate or fat is present, and that this difficulty does not interfere with the utilization of the energy of alcohol (181).

Pyridoxine

Pyridoxine is needed by all animals thus far studied Its deficiency in animals finds expression in inhibition of growth, dermatitis, edema, muscular weakness, convulsive seizures, and microcytic anemia A biochemical defect observed in pyridoxine-deficient animals, the increased excretion of xanthurenic acid, especially after ingestion of tryptophane, proved useful in assessing deficiency in the human Evidence that it is essential for the human being is now available (182) The human animal, too, excretes increased amounts of xanthurenic acid on pyridoxine deficient diets (183) Increased blood urea in response to a test load of *dl*-alanine is a useful index of pyridoxine deficiency (182) In normal human subjects increased blood urea levels return to normal values within 12 hr In hyperemesis gravidarum, the high blood urea levels failed to decrease between the sixth and the twelfth hours. Administration of pyridoxine restored urea responses to normal

Two infants on a pyridoxine-deficient diet plateaued in weight. One developed convulsions which were promptly cured by pyridoxine The other developed hypochromic anemia which responded to pyridoxine with reticulocytosis after 72 hr, reaching a peak in four days, after which the red cell count and hemoglobin rose to normal (184)

The clinical manifestations of pyridoxine deficiency find roots in the enzyme systems of which it forms a component part It has been demonstrated that pyridoxine is the coenzyme of enzyme systems that decarboxylate amino acids, racemize, transaminate, and deaminate them It is also a

dren develop atrophy of the enzyme-secreting cells of the pancreas, and fatty liver ensues as a consequence of what is virtually a dietary depancreatization. The pancreas and other secretory organs respond to protein rich diets, especially milk protein It is doubtful that any specific response has been demonstrated to methionine, choline, vitamin B_{12} or folic acid (167). Desiccated stomach powder (ventriculin) was particularly beneficial (169).

Secretion of hormones of the small intestine is more likely to fail in infants than in adults, explaining the great difference between infants and adults in the susceptibility of the pancreas to malnutrition. Fatty liver in a human subject was said to result from atrophy of the pancreas, which was ascribed to surgical removal of the small intestine with resulting deficiency of the intestinal hormones, secretin, and pancreozymin (170) The following sequence of events is suggested for the development of liver cirrhosis Failure of the hormonal secretions of the small intestine, failure of the external secretions of the pancreas, failure of proper digestion of proteins and release of sulfur amino acids, fatty liver

Pregnancy predisposes women to liver injury. Demands by the fetus for nutrients, or gastrointestinal disturbances, if associated with faulty diets, produce a situation analogous to that in rats given diets marginal in casein or choline and then allowed to become pregnant. Gross fatty liver develops After parturition the fat content returns to normal, explaining perhaps why diffuse hepatic fibrosis does not develop (95). The recently discovered role of pyridoxine deficiency in pregnancy (discussed in another section) may be associated with liver injury

Alcohol.—In 1942, on the basis of existing information, it was concluded that alcohol could not be considered in any sense a food (171) Recent work has altered this conclusion The ability to metabolize alcohol resides almost exclusively in the liver (172). The liver is capable of synthesizing fatty acids and cholesterol from ethyl alcohol, thus metabolizing alcohol as a food probably via acetic acid Almost the entire metabolic load of alcohol is thrown upon the liver. The oxidation of alcohol is directly proportional to the dose up to a maximum of about 3 gms per kilogram, after which if the dose is increased the rate of oxidation decreases (173). Fasting markedly decreases the rate of alcohol oxidation both *in vitro* and *in vivo*, and this is interpreted as resulting from loss of liver enzymes necessary for oxidation of alcohol. Rats forced to consume alcohol decrease food intake by the number of calories they consume as alcohol, so that total caloric intake is the same Their growth is the same, showing that alcohol is used to promote growth (174, 175) On low protein diets alcohol cannot spare protein (176) Liver injury did not occur when alcohol was fed to rats in addition to an adequate diet (149, 174)

In the human being alcoholism and cirrhosis of the liver have long been associated The assumption first made, that alcohol acted by a direct toxic action on the liver, was rendered uncertain by failure to produce cirrhosis in animals on adequate diets by the administration of alcohol. This fact,

acids was demonstrated in human beings with results comparable to those in rats. Pyridoxine-deficient subjects with dermatitis were cured of their skin lesion with essential unsaturated fatty acids which, at the same time, were without effect on glossitis and neuritis (190).

Studies with rats revealed an interrelationship of methionine with pyridoxine On pyridoxine-deficient diets methionine depressed growth at levels normally supporting optimum growth (193). One of the effects of excess methionine is to aggravate a pyridoxine deficiency (194)

Diets high in protein increase pyridoxine requirements, presumably by their content of sulfur containing amino acids (194) This is in sharp contrast to pantothenic acid deficiency, in which high levels of either protein or methionine are beneficial (195, 196).

Studies with rats showed that antibody responses to injection of antigens were severely impaired in pyridoxine deficiency, as well as in deficiencies of folic acid or pantothenic acid (197)

Mild normocytic anemia in seven patients did not respond to pyridoxine, indicating that the adult human like the rat is refractory to pyridoxine-deficiency anemia, in contrast to the dog, pig, and human infant who develop marked microcytic anemia Pyridoxine, when applied locally, healed skin lesions The healing takes place only at the site of application (190). It must therefore be absorbed and utilized by the skin

Observations on pyridoxine metabolism in pregnant women were made by studying the xanthurenic acid excretion after tryptophane administration. The average excretion of xanthurenic acid in 14 normal women was 14 mg.; in 100 uncomplicated cases of pregnancy, 195 mg ; and in 16 cases of toxemia of pregnancy, 285 mg. Administration of 25 mg of pyridoxine promptly restored the xanthurenic acid excretion to normal (198) In studies on continued administration of pyridoxine it was found that 2 5 mg daily was ineffective, 3 3 or 5 0 mg daily was not effective in all cases, while 10.0 mg daily was fully effective It was suggested that pregnant women be given 10 0 mg of pyridoxine daily to meet their increased requirement (198)

Further evidence of human pyridoxine deficiency appeared in the observation of convulsive seizures in infants subsisting on a processed milk formula The convulsions were cured by pyridoxine administration (199, 200). Other infants on this type of formula, assayed to contain about 0 18 mg of pyridoxine per liter, developed convulsions, and they were cured when given an evaporated milk mixture containing 0 26 mg of pyridoxine per liter (201) When a change from 0 26 mg /liter of pyridoxine to 0 18 mg /liter results in convulsions, then the factor of safety is indeed low.

An electroencephalogram obtained during status epilepticus showed a characteristic convulsive pattern. About 1 min. after injection of 100 mg. of pyridoxine, the electroencephalogram improved and, after 4 or 5 min , reverted to a normal sleep record. The convulsions had ceased (200)

A striking finding in the pyridoxine-deficient rhesus monkey, potentially

component part of enzyme systems that act as desulfhydrases and transsulfurases, and it participates in some manner in the conversion of linoleic to arachidonic acid (185, 186).

Growth hormone aggravates the manifestations of pyridoxine deficiency (187). Pyridoxine-deficient rats showed morphologic changes in the adrenal cortex, predominantly involving the zona fasciculata (188). Pyridoxine-deficient rats showed increased brain excitability with lowering of the electroshock threshold. Pyridoxine injection caused the threshold to rise, and glutamic acid facilitated this process. It was concluded, "the maintenance of normal transaminase activity is essential for those tests of normal brain activity employed *in this study*" (189).

Pyridoxine deficiency has been studied in human subjects using the pyridoxine antagonist, desoxypyridoxine (190). Of 50 patients, 34 developed symptoms of pyridoxine deficiency. The results are in accord with the versatility of pyridoxine in the number of metabolic processes in which it participates The signs that develop are those usually found in vitamin B complex deficiency states.

Anorexia and drowsiness were the most common subjective symptoms of pyridoxine deficiency. Many patients developed moderate nausea and vomiting. Some became lethargic, somnolent, and confused. Weight loss was common, probably because of loss of appetite and decreased efficiency of food utilization (191). Administration of pyridoxine, pyridoxal, or pyridoxamine met with striking responses Within 12 hr the patients felt better, nausea disappeared, and appetite improved Lesions disappeared rapidly (190)

Severe neuropathy occurred, simulating the neuritis of thiamin deficiency; glossitis, stomatitis, and dermatitis simulated the lesions of nicotinic acid deficiency. Seborrheic dermatitis of the nasolobial folds, buttocks, scrotum, perineum, and facial lesions of cheilosis, angular stomatitis, and conjunctivitis, all described as characteristic of riboflavin deficiency, occurred in the pyridoxine-deficient subjects These lesions responded only to pyridoxine and to none of the other members of the vitamin B complex Convulsions were not reported (190), suggesting a difference from the human infant that does develop convulsions

Biochemically, these pyridoxine-deficient subjects responded as anticipated from work with other animals, with increased excretion of xanthurenic acid after tryptophane administration, and elevated blood urea levels after the *dl*-alanine load tests Both returned to normal after pyridoxine administration (190).

Of particular interest was one patient with glossitis that did not respond to nicotinamide, but did respond to cozymase within 24 to 48 hr This confirmed work with animals that cozymase, though containing nicotinamide as a component part, is synthesized not from nicotinamide but from tryptophane, and that pyridoxine is essential in the process (192).

The interrelationship of pyridoxine to the essential unsaturated fatty

fetus is not known Any nutritional disturbance which interferes with the production of these hormones during the seventh to eleventh day of pregnancy results in fetal death and resorption. Four such nutritional disturbances have been demonstrated; namely, deficiency of protein, pyridoxine, thiamine, or potassium (212)

Protein Deficiency.—Pregnancy can be maintained in rats on a protein-deficient diet by injection of estrone and progesterone (212, 213). Maintenance of pregnancy in protein-deficient rats was possible by injection of progesterone alone (212, 213). The success, if estrone alone was used, depended upon the level used Injection of 1 μg. maintained pregnancy in 60 per cent, 2 μg daily in 80 per cent, 3 μg in 73 per cent, but 6 μg. daily did not maintain pregnancy in protein-deficient rats at all (212, 213). Imbalance among hormones appears to be of no less importance than imbalance in nutrients

Thiamine Deficiency.—Pregnancy can be maintained in the thiamine-deficient rat by a combination of estrone and progesterone. Progesterone alone maintained pregnancy in 73 per cent, but estrone alone had little effect (214)

Pyridoxine Deficiency—In pyridoxine-deficient rats resorption occurred on the tenth and eleventh days A combination of 1 μg of estrone and 4 mg. of progesterone maintained pregnancy in 90 per cent of the rats, whereas either one alone resulted in 90 per cent resorption The results clearly indicate an inadequacy of secretion of ovarian hormones in pyridoxine deficiency (215) The balance between progesterone and estrone was of decisive importance. When progesterone was maintained at 4 mg daily and the estrone increased to 2 or 3 μg daily, pregnancy was maintained in only one-third of the rats, and when estrone was increased to 6 μg there were no fetal survivors.

Pyridoxine deficiency causes dysfunction of both pituitary and ovary This was demonstrated by a series of ingenious experiments using various combinations of pituitary and gonadal hormones (216) There was no deficiency of follicle-stimulating hormone since the anterior pituitary of the pyridoxine-deficient rat had about seven times as much of this hormone as the normal rat Similarly the protein-deficient rat has about three times as much follicle-stimulating hormone in its pituitary as does the normal (212).

Many nutritional disturbances do not arrest processes so vital to the fetus that it dies, instead it survives with varying degrees of injury, to be born with various types of congenital anomalies The type and severity of the anomaly depends upon the stress imposed, the time during gestation in which it acts, and to some extent on the type of nutritional disorder

The role of nutritional deficiencies in the production of congenital abnormalities has been comprehensively reviewed (206, 216, 217). Excess vitamin A has also been shown to produce congenital anomalies, in many respects similar to those produced by a deficiency of vitamin A In addition, presumably due to the increased severity of the stress imposed, excess vitamin A fed

of great importance in human nutrition, is the occurrence of arteriosclerosis resembling that occurring in man (202). This important finding has now received confirmation (203).

Except in pregnancy and in infancy, there are no definite data on the human requirement for pyridoxine. In monkeys, the requirement for maximum growth is about 80 µg. per kg. of body weight (204). If a similar figure applies to man, a human weighing 70 kg. needs about 5.0 mg. of pyridoxine daily, which is considerably more than is contained in many diets regarded as being good in protective factors. Since enriched flour does not include pyridoxine, the margin of safety may be low in the United States

Gestation

Inadequate nutrition of the mother may prevent or arrest developmental processes. In 1921 it was found that arresting fetal development at certain precise times was accompanied by injury to the fetus. These have been termed "critical moments."

> . . . When an important organ is entering its initial rate of rapid proliferation, a serious interruption in the developmental processes by temperature changes or anoxia often causes decided injury to this particular organ, while slight or no ill effects may be suffered by the embryo in general (205).

In rats, in which congenital abnormalities have been studied most extensively, implantation occurs seven days after mating. A critical period begins with implantation and ends on about the fifteenth day. The accumulating evidence confirms the postulates advanced in 1921 that the primary action of all noxious agents is to inhibit the rate of development, and the type of resulting deformity depends upon the developmental moment at which the interruption occurs Congenital deformities may occur with defective nutrition (206, 207), anoxia (208), or radiation damage (209), and thus are not completely specific

"During the critical period of fetal organogenesis the placenta undergoes crucial differentiation" (210) During this period the fetus depends upon the mother for vital compounds later supplied by the placenta Two such compounds vital to survival of the fetus in its early stages are estrone and progesterone Hypophysectomy before day 11 quickly terminates pregnancy, but not if performed after day 11 (211) If estrone and progesterone are denied to the fetus by either hypophysectomy or oophorectomy, between the seventh and eleventh days, the fetus dies and is resorbed Administration of estrone and progesterone to the hypophysectomized animal makes maintenance of pregnancy possible (211) After the eleventh day the placenta presumably takes over the role of the hypophysis and makes estrone and progesterone available to the fetus, either by direct formation of these compounds or by producing gonadotrophic hormones which stimulate the ovary to secrete them Whether estrone and progesterone act directly on the fetus, or stimulate the maternal organism to produce compounds essential to the

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during the seventh to the tenth day of gestation produced severe brain injury, namely exencephaly, and hydrocephalus (210). Similar brain injuries, including anencephaly and a host of other congenital anomalies, were also produced by the folic acid antagonist x-methyl pteroylglutamic acid when administered to rats on folic acid-deficient diets (218). The exacerbation of congenital anomalies in nutritionally deficient rats by metabolic inhibitors is further illustrated in riboflavin-deficient rats Defects, predominantly skeletal, *were observed in rats on riboflavin-deficient diets (206, 217), but* when the administration of the riboflavin-antimetabolite galactoflavin imposed an additional stress, widespread defects in the soft tissues were observed in addition to skeletal damage (218).

These studies emphasize the importance of a satisfactory nutritional state of the mother in the earliest periods of pregnancy. The organogenesis of the human embryo is practically finished ten weeks after conception, at a time when the expectant mother is not accorded any special privileges, since nutritional supplements are not as a rule given before the second half of pregnancy (206). The task of the pediatrician starts at the beginning of pregnancy and not at the end

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ALLERGY AND IMMUNOLOGY[1]

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INTRODUCTION

During the year ending July, 1954 there have been no outstanding events such as the introduction a few years ago, of the antihistamine drugs and a year or so later, the discovery of hormones, cortisone from the adrenal cortex, and the anterior pituitary stimulant for the adrenal cortex known as ACTH. These therapeutic agents have been studied carefully and evaluated as to their uses, dosages, contraindications, and untoward effects One of the more interesting conclusions in hormone therapy is that these drugs may be used over prolonged periods in proper maintenance doses. This is of great benefit in certain cases in which the etiology is not known, e g , periarteritis nodosa, and in others of known cause that do not yield to other forms of treatment The original hope that the results from hormone use would throw light upon still unknown basic factors operative in the production of antibody and reaction of it with antigen in artificial and spontaneous sensitization of man and animal has not materialized. Actually, little is known of just how the hormones act to secure the obvious clinical improvement.

On the other hand, there has been continued study in the basic spheres of immunology and allergy (hypersensitivity), and some advance has been made along lines of the conventional immunological approach. These have stimulated continuing interest in the quest for solutions of the many remaining enigmas in the field For example, the existence and possible importance of a proteolytic enzyme system as fundamental in the production of allergic manifestations and of anaphylaxis in particular has received impetus from the work and review by Burdon and other workers in the same field.

Another contribution that stimulates a review of the ideas on causes of allergic disease is that of Rammelkamp who relates certain cases of nephritis to the type 12 hemolytic streptococcus This association of disease with one specific type of coccus is a good illustration of the difficulties of research and how easily confused and conflicting results may be obtained since the materials we work with are so complex and but vaguely characterized. The roles of infection in allergic diseases will be discussed as will such other factors as auto and iso sensitization that may be fundamental in clarifying the reactions we believe may be manifestations of clinical allergy, with special emphasis on the more recent work.

We shall then turn attention to a group of diseases for which hypersensitiveness has been suggested as a possible solution for their unknown patho-

[1] The survey of the literature pertaining to this review was completed in July, 1954.

genesis. Only the immunological aspects will be considered in disseminated lupus, the purpuras, and multiple sclerosis for there has been considerable recent work on these diseases.

Another field in which there is recent activity is that of homografting of tissues, because of the immunological implications that may ultimately have wide application in tissue and organ transplantation.

Finally, another field that will be reviewed is that of respiratory function which, though by no means new, is commanding widespread interest among physiologists and clinicians interested in allergy on account of its bearing on asthma and emphysema resulting from allergies of the respiratory tract. It must be admitted, however, that perhaps the major stimulus to these studies comes as a result of the increasing amount of intrathoracic surgery.

THE ALLERGIC PHENOMENA

For purposes of discussion the allergic phenomena will be divided into two generalized reactions, anaphylactic shock and the Shwartzman phenomenon, and a collection of local reactions, the separation between which is not always clear In addition the nonspecific C-reactive protein response and the newly discovered protective serum protein, properdin, will be mentioned

Generalized anaphylactic shock —Burdon (1) and others have become concerned with the function of the proteolytic enzyme systems of the blood. He postulates that it is the activation of these enzymes that is the basic factor in the production of anaphylaxis and that histamine is only one of the results of this activation This idea is not new, having been supported over a long period by Bronfenbrenner (2 to 6) However, Burdon's monograph has revived the interest, and he has restated the evidence, adding some of his own observations

In reviewing the theories of the mechanism of allergic responses he does not separate the generalized anaphylactic state from the localized phenomena on the grounds that the basic process is probably the same for all allergic reactions.

He presents three theories of allergy The cellular theory, in which symptoms are attributable to the release of preformed histamine, acetylcholine, heparin, and other metabolites as a direct result of cell injury by antigen combination with the cell fixed antibody The humoral theory, in which anaphylatoxin or serotoxin is thought to be released from the body fluids by the antigen-antibody combination Lastly, he presents the theory to which he himself subscribes and which he calls the protease activation theory. In the body fluids and in the tissues there are proteolytic enzymes and precursors of proteolytic enzymes existing in balance with antiproteolytic factors The protease activation theory maintains that the antigen-antibody reaction occurring either in the blood or locally in the tissues acts as a trigger mechanism for the activation of these enzymes They in turn cause cell damage releasing histamine, acetylcholine, and other products, giving rise to anaphylactic shock and probably to other allergic manifestations He ar-

at considerable length against the importance of cellular fixation of antigen because he feels strongly that anaphylactic shock may be produced when unattached antibody in the circulation or locally reacts with antigen. The localization of antibody will be discussed later so it will suffice to say that antibody often does remain in one place for a period of several weeks or months, suggesting that it is either attached to or contained in cells. Evidence at hand certainly does not prove that this is so, for antibody may simply not be carried away. However, experience of such phenomena as antibody coating erythrocytes (as in Coombs test) lends weight to the idea that surface phenomena may have a role. The concept that cell-united-antibody is the only antibody capable of reacting with antigen to cause cell damage is not so convincing a thesis that another cause of the damage such as proteolytic activity might not be the explanation Whether antibody is attached or not, the importance of localization and distribution of antibody in places where it is most likely to cause manifestations should not be minimized

To support the protease activation theory Burdon gives the following positive evidence from his own work: (*a*) A sudden drop in the protease-inhibiting capacity of the blood usually shown at the time the symptoms of anaphylactic shock are beginning; (*b*) The presence in the body fluids of an abnormally high concentration of protease inhibitor, regularly found when an animal is refractory, (*c*) An increased titer of active blood plasmin measurable at the height of the shock; (*d*) Homologous inhibitor-free proteolytic serum which induces in guinea pigs, when injected intravenously, the characteristic symptoms and gross pathology of anaphylactic shock

From the work of others, particularly the work of Rocha e Silva, he adds considerable evidence The following is a summary of some of the work he cites: (*a*) Felberg & Kellaway (7) perfused lung with a proteolytic material (cobra venom) and found that histamine was released in amounts comparable to those in anaphylactic shock. (*b*) Rocha e Silva *et al.* (8 to 19) compared the action of snake venoms, trypsin, and peptone with the reaction to antigen and attributed the similarity of their action to the liberation of histamine and similar smooth muscle stimulating substances (*c*) The development of the refractory state to antigen-antibody challenge after peptone shock was noticed by various investigators. (*d*) Rocha e Silva & Teixeria found increased activity of the "plasma trypsin" after peptone shock. It was decreased after hyposensitization with peptone. (*e*) Scroggie & Jaques collaborating with Rocha e Silva did further work in which the activation of serum protease in peptone shock was studied. They showed an increase in proteolytic activity within 2 to 8 min. after injection of peptone This activity could be inhibited by soybean trypsin inhibitor *in vitro*, and both the symptoms of shock and the increased proteolytic activity could be reduced by giving the animal this inhibitor intravenously before the peptone. (*f*) When sensitized liver or lungs were perfused with Tyrode's solution instead of whole blood the addition of antigen or peptone released much smaller amounts of histamine than when whole blood was used. (*g*) Unger & Mist

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Waksman & Bocking (26) have followed the fate of bovine gamma globulin and of crystalline egg albumin using fluorescent antibody. They have found that after intracutaneous injection in animals the antigen is seen in the histiocytes locally and in the regional lymph nodes. Considerable amounts remain extracellular and are not phagocytosed by granulocytes although these are present. Fluorescent material (antigen-antibody) is also seen in many lymphoid cells and in the tissue histocytes In passively sensitized animals and in animals actively sensitized with antigen and Freund's adjuvant the disappearance of the antigen from the skin and from the lymph nodes is slowed. The role of lymphoid cells in tissue defense has been puzzling for a long time. The presence of antigen within them both locally and in the lymph nodes is interesting. Considerable evidence that the lymphocytes play a major role in the formation of at least some antibodies has accumulated. Chase (27) states that this is particularly true in the case of intracutaneous inoculation of antigen.

The delayed reactions in the skin have been of particular interest this year because of further attempts to transfer this type of sensitivity. Chase (28) has transferred antibodies to diphtheria toxin by transferring lymphocytes He has found that antibody appearing in the recipient has the avidity properties characteristic of the period in the immune response reached by the donor at the time the cells were taken.[2] The immune response carries on from there in the recipient in the same pattern as it would have done in the donor. A later stimulating dose of toxoid will not produce an anamnestic response in the recipient of the cells but instead only the normal response to an initial dose of toxoid This work suggests that once a generation of lymphocytes has been sent on its way to produce a certain antibody response it will continue in a distinct pattern The fact that this occurs even when the lymphocytes are removed to a foreign milieu or carry it within themselves is something that may well have clinical meaning. If one wishes to speculate beyond known evidence, one could hope that in those conditions where it is suspected that an antibody response is pathogenic some method of eliminating a generation of lymphocytes might prove successful in treatment if further stimulation could be removed or response inhibited

Chase (27) has also transferred sensitivity to certain chemicals by transferring lymphocytes Haxthausen (29) believes that he has transferred cutaneous sensitivity to certain metals in the human subject by intracutaneous injection of lymphocytes from sensitive individuals, but he comments that the mere transfer of lymphocytes causes local tissue reaction of sufficient degree to make interpretation of his results difficult. Lawrence (30) has continued his experiments, transferring tuberculin sensitivity by intracutaneous

[2] When a large and a small dose of toxin are given intracutaneously to a rabbit, the difference in the amount of antitoxic serum required to counteract the two doses is a measure of the avidity of the antitoxic serum being tested Normally this difference is greater at the beginning of the immune response and, as the response continues, it becomes less because the antitoxin becomes more avid and is able to neutralize the larger dose of toxin more easily

(20) found that proteolytic enzyme precursors were changed to the active form in serum of sensitized animals by antigen. (*h*) Clifton (21) demonstrated increased proteolytic activity in dogs within 2 min. of sublethal shocking dose of antigen. On the contrary, Geiger (22) showed increased activation of plasminogen in the plasma of sensitized rabbits given antigen but he considered it unlikely that anaphylactic symptoms in rabbits could be attributed wholly to this. Further, McIntire *et al.* (23) recently reports that he was unable to demonstrate increased proteolytic activity in anaphylactic shock in the rabbit.

All this adds up to a considerable amount of evidence in favor of a role for proteolytic enzyme activation in the generalized reaction of anaphylactic shock, and further studies will be awaited with great interest.

Localized allergic phenomena.—There is no real evidence as yet that the proteolytic-antiproteolytic systems play a part in the localized phenomena of allergy. Since such systems exist in the tissues (24, 25) as well as in the blood, the extension of the theory to include them or at least some of them is very tempting. There is obviously much work to be done.

Antibody localization and local allergic reactions are of great clinical importance because so many of the clinical allergies probably fall into this group The inhalant allergies, the skin contact allergies, many food allergies, and perhaps even the so-called intrinsic or infective cases all are reacting on external or internal body surfaces whose normal function is to provide a more or less selective barrier between the tissues and the outside world. In these conditions circulating antibodies may be present in such quantity that a very small injected dose of allergen will produce signs of generalized anaphylaxis but even so, in the clinical diseases, e g , hay fever, the barrier retains its integrity, and signs of generalized reaction are very rare.

Comment is due on the subject of the specific as opposed to the non-
[illegible] the desensi-
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[illegible] s country.
While there are cross reactions or presumably common antigens which made specific hyposensitization in the human being not completely specific, and while there may be a degree of nonspecific desensitization, the latter does not appear to play a major role in the success of therapy It is not uncommon, for example, to treat ragweed hay fever successfully by the perennial method and have the same patient develop severe symptoms from grasses several years later while still receiving large doses of ragweed It might be argued that grasses are more potent antigens but the reverse sequence also occurs

Skin-sensitizing antibody in human blood does not necessarily give rise to the symptoms of respiratory allergy, and the respiratory tract may react to only one of the two inhalant allergens apparently equal in terms of skin tests in the same individual What determines whether hay fever will occur or not is unknown. It is tempting to think of the reason as probably local in nature and because of the fact just mentioned, probably both specific and local

The use of adjuvants of the type used by Freund containing killed tubercle bacilli, falba or aquaphore, and mineral oil, has continued to prove very useful in producing autosensitization. Lipton & Freund (36) find that myelitis can be produced in several animals using a single dose of central nervous system tissue with this adjuvant. Chase (37) has successfully used these adjuvants with certain simple chemicals such as picryl chloride intraperitoneally or intramuscularly and produced a dermatitic sensitivity to these compounds when applied to the skin.

The Shwartzman-Sanarelli phenomenon.—This phenomenon is observed in a generalized form and in a local form. The local phenomenon is produced by a local injection of bacterial filtrate (also other substances) followed 8 to 32 hr afterwards by a small intravenous dose of the same or unrelated material. The result is a hemorrhagic necrosis caused by thrombosis and disruption of blood vessels at the site of the preparatory injection.

The general Shwartzman (38, 39) reaction is produced in the same way except that the preparatory dose as well as the provocative injection is given intravenously. The thrombosis and hemorrhagic necrosis in this case is found in the kidneys, lungs, liver, heart, etc. In pregnant rabbits and in animals which have received large doses of cortisone the reaction may occur with the provocative dose only and without any previous preparatory dose.

The clinical interest in these reactions lies in the similarity of the lesions produced by them to those of eclampsia and certain drug and antibiotic reactions (40). McKay *et al.* (41) feel that the bilateral cortical necrosis, liver lesions, pituitary necrosis, and premature separation of the placenta may all be manifestations of this phenomenon. Good & Thomas (42) report that the reaction can be inhibited by heparinization of the animal before the provocative material is injected but not if heparin is given after provocation.

Other basic allergy problems.—The other basic problems that remain to be discussed concern the difference between the allergic individual and the normal. With a very incomplete knowledge of antibodies themselves and a partial knowledge of where they come from we are confronted with questions in which there are still far too many unknowns.

The role of various cells in antibody production remains confused, with the lymphocyte and the plasma cells favored as probably the most active. There are two studies reported on the production of antibodies in patients with lymphomas, one by Larson & Tomlinson (43) and another by Geller (44). It appears that antibody production is increased in acute leukemia and reduced in chronic lymphatic leukemia and lymphosarcoma. Hodgkin's disease gives more variable results. If antibody formation is connected with the production of new lymphocytes, this fits in with the findings in acute leukemia and with the probability that both production and destruction of lymphocytes are markedly impaired in the chronic condition.

Thorbecke & Keuning (45) have measured the antibody produced by tissue cultures of spleen, liver, bone marrow, lymph nodes, and thymus from animals immunized with paratyphoid B. They found that with this technique the spleen produced the most antibody. The bone marrow and lymph

injection of buffy coat. He is able to transfer this type of sensitivity with a resulting skin reactivity not localized to the site of cell injection. Characteristic tuberculin reactions can be elicited in the opposite arm for as long as several months after the transfer. This does not appear to be the same phenomenon as lymphocyte transfer because Chase had to use healthy living cells and the resulting sensitivity was comparatively transient On the other hand, Lawrence was able to obtain the same prolonged state of sensitivity whether or not the cells have first been digested with desoxyribosenuclease or ribosenuclease. These differences are puzzling and serve to emphasize the gaps in our knowledge.

Other local manifestations of allergy are those produced in the laboratory by autosensitization. Some of the diseases in which it is thought that this plays a part will be discussed elsewhere. Korngold & Pressman (31, 32, 33) have developed a method of purifying autoantibodies They found at first that they could obtain samples with increased specific localizing properties by adsorbing the antibody onto fractions of the homologous tissues, i e, spleen, liver, kidney, etc., and then eluting the antibody. This worked quite well, but they found that if the material was first adsorbed into fractions of other tissues and then removed and adsorbed into the homologous tissue they could produce samples whose specificity was very much greater. In this way they have made preparations of anti-tumor antibodies that will localize almost entirely in tumor tissue as traced by radioactive iodine. The same authors and associates have isolated from homogenates of kidney tissue substances with strong power to neutralize anti-kidney antibody. These they believe are probably the substances responsible for localization in the kidney

Fitch *et al* (34) have studied the localization and disposal of radioactive iodine-marked typhoid vaccine in the spleen of the rat with special reference to the effect of radiation They have found that the phagocytosis and distribution of the vaccine is the same in normal, x-irradiated, and x-irradiated with spleen shielding However, there is an increase in the red pulp that occurs in the normal animals and in the spleen-shielded ones which does not occur in those whose spleens have been damaged by x-ray.

Taking a broad viewpoint, the destruction of granulocytes by the antigen-antibody reaction might belong in the category of local allergy because of the specificity of the cell destruction. Attempts to observe lysis of the granulocyte in this situation have continued Waksman (35) has observed it *in vitro* with the combination of rabbit anti-bovine gamma globulin and its antigen. He states that the leucolytic power was moderately well correlated with the ability of this serum to passively sensitize human skin, but not with its ability to produce anaphylaxis in the guinea pig. Whether this lysis represents activation of local proteolytic enzyme systems or simply the proteolytic activity that would be expected when cells, whose function is digestion, are damaged is not clear. However, it is of note that the cells appear to be damaged because to date there has been much conflicting evidence in attempts to use leukocytolysis both *in vitro* and *in vivo* to show the presence of allergy.

TABLE I

Comparison of Antibodies to Ragweed Pollen and Diphtheria Toxin

	Passive Transfer Skin	Destroyed at 56°C for 5 hr.	Passive Arthus	Complement Fixation	Anaphylaxis	Precipitation
Ragweed						
Skin Sensitizing	+++	Yes	No	Slight	No	0
Blocking	0	No	?	Slight	?	0
Diphtheria						
Nonprecipitating	+++	Yes	No	Slight	Yes	0
Precipitating	0	No	Yes	Marked	Yes	Yes

antigens governing the production of these different types of antibody in response to a given stimulus will do much to increase our understanding of the causes of allergy (54) The studies that have been mentioned in this section represent such a small part of the research being done in this field that they are only offered as examples of the kind of work being done.

The role of heredity in human allergy is discussed at length in a critical review by Ratner & Silberman (55) Their general conclusion is that the part played by heredity in the majority of cases is still not at all clear They quote at length from the recent monograph by Schwartz (56), who found that bronchial asthma was a genetic entity and that in this respect intrinsic asthma and extrinsic asthma were indistinguishable The latter finding agrees with earlier findings of other authors (57) Genetically related to asthma were vasomotor rhinitis and probably cases of infantile eczema in which a definite allergen was found Urticaria, angioneurotic edema, gastrointestinal allergy and contact dermatitis did not appear to be hereditarily related to asthma. In his study of 50 cases of baker's asthma, Schwartz (56) felt that the results did not warrant the conclusion that all cases of this type of asthma were necessarily on an hereditary basis Ratner's review concludes that there is as yet no satisfactory demonstration that the ability to become sensitized "within the scope of the antigen-antibody mechanism" is genetically controlled For instance, the cause of apparently hereditary susceptibility may be inheritance of a susceptible respiratory tract The work of Kuhns (48), in which the antigen was entirely given by injection and in which retention seemed to be different, apparently on a familial basis, would be interesting in this respect if it can be confirmed by other workers

Chase (37, 58) has found that heredity influences the production of sen-

nodes also produced it but less actively, and the thymus and liver did not produce any at all.

Berglund (46) has measured antibody production after a single dose of typhoid H vaccine. He found that cortisone given daily, four days before antigen injection, reduced the response while if it was given the third to the sixth day when the titer was rising rapidly there was no effect. The same was true from the seventh to the fifteenth day when titers were constant.

Inhibition of antibody formation in the adult by very early or prenatal doses of antigen (bovine albumin) in rabbits has been observed by Hanan & Oyama (47). This inhibition has many possible implications, and it would be interesting to know whether any detectable antibodies other than precipitins are formed as the tests done by Hanan were for precipitins and the Arthus phenomenon

There are some recent interesting studies on the nature and production of skin sensitizing antibodies Kuhns & Pappenheimer (48 to 51) have been studying the antibody response to a booster dose of diphtheria toxoid in a group of medical and dental students. In their first study of this group they tried to correlate the occurrence of nonprecipitating skin sensitizing antibody with immediate skin reactions and with the allergic history of the subjects. They found that there was a high degree of positive correlation between the presence and quantity of nonprecipitating antitoxin and the degree of skin sensitivity of the immediate type They examined 131 previously immune students before the booster dose Of the 59 of these giving either personal or family history of allergy, 60 per cent showed an immediate skin reaction to toxoid whereas among the 72 who denied all knowledge of allergic history only 5 per cent showed such a reaction This striking difference between the two groups was not found when the students were retested after the booster dose This suggests that there may be a difference in retention of the nonprecipitating antibody over a long period of time in the allergic group rather than a difference in antibody formation.

Kuhns then studied properties of the nonprecipitating skin sensitizing antitoxin, comparing it with the precipitating antitoxin formed in response to diphtheria toxoid. He found that the nonprecipitating antibody had many of the properties of the skin sensitizing antibody formed in the spontaneous pollen sensitive patient The precipitating antitoxin also had some properties in common with the blocking antibody found in patients treated with pollen extract.

The fact that two quite distinct antibodies are separable in various other situations has been noted for a long time and is mentioned in early observations as long ago as 1929 by Cooke & Spain (52). In 1951 Sherman *et al* (53) studied the properties of nonprecipitating antibody formed in rabbits in response to ovalbumin. The properties of this nonprecipitating antibody were also very similar to those in Kuhn's more recent studies. It is likely that a better knowledge of the stimuli and conditions or the composition of the

in localization is well demonstrated in the work of Fazekas de St. Groth (62) studying with Burnet in Australia He was working on experimental influenza in mice and found that, if he immunized them intraperitoneally and at the same time caused a mild inflammation of the bronchi with any one of a wide variety of substances, the amount of antibody in bronchial washings was greatly increased and also the immunity to intranasal infection with virus This increase lasted only as long as the inflammation lasted. If we fit the clinical allergies into these categories we find that many cases as well as those where the organisms act as antigens could be affected by infection in other ways.

Here again there are many unknowns, but because of the experience that the onset of allergic symptoms may be immediately preceded by acute infectious disease and because the whole group of "intrinsic" asthmas are in some peculiar way linked with infection, a great deal of work is needed to clarify these relationships

Nonspecific immune substances—The C-reactive protein response is a nonspecific response which is attracting increased attention both as a practical clinical test and because of its probable importance in immunology. The name given to this substance refers to the fact that as a result of many nonspecific stimuli there appears in the blood a protein that reacts with the pneumococcal somatic carbohydrate known as "C." This protein is produced rapidly after the onset of infections or within 24 hr. of the injection of a large number of substances including foreign proteins, india ink, and a collection of antigenic and nonantigenic materials In the case of infection the level of C-reactive protein seems to parallel the degree of tissue damage rather as the sedimentation rate does, but is more sensitive and probably more accurate. Studies of its use in rheumatic fever (63) suggest that this test may well replace the sedimentation rate as an index of activity. This protein is of interest to the immunologist and allergist because it is one of the responses to many of the things we do experimentally and therapeutically. It may also have meaning in connection with the immune response. There has been a suggestion that it may be a percursor of antibody and necessary for its manufacture. In support of this is the finding of Wood (64) that in rabbits the Cx[3] reactive protein response gives a good indication of what the later precipitin response of the same animal will be The same worker has studied the effect of the various components of Freund's adjuvant on C-reactive protein response He finds that aquaphor produces a marked rise, mineral oil a lesser one, and killed tubercle bacilli none at all. This suggests that the various components of this adjuvant may stimulate separate parts of the immune mechanism.

Another nonspecific immunologically active substance has just been described by Pillemer *et al* (65) He calls this new blood protein properdin and states that it is found in the blood as a naturally occurring immune sub-

[3] In the rabbit the protein reacts with a slightly different carbohydrate also from the pneumococcus and is designated Cx reactive protein.

sitivity to simple chemicals such as picryl chloride in guinea pigs He also finds that it affects susceptibility to enhancement of sensitivity by Freund's adjuvant. The two are not necessarily parallel in the same animal.

Having considered the part apparently played by heredity in the etiology of human allergy we are lead to a comparison with certain diseases that have also shown hereditary tendencies such as tuberculosis, rheumatic fever, and nephritis. In these, although infectious agents were known, or in the latter two cases suspected of being involved, there seemed to be either a hereditary susceptibility to the organism or a hereditary tendency to react in a certain peculiar fashion to the organism. In this regard it is of note that in the series of cases described by Ratner the incidence of allergy in children was greater when there was allergy in the family, but it was no greater when both sides of the family were allergic than when only one side was so affected.

Rammelkamp and his associates (59) have found that among the very large number of streptococcal infections that they studied, acute nephritis was caused almost entirely by hemolytic streptococcus types 12 and 4, particularly the former Recently a similar study by Wilmers *et al.* (60) in Great Britain showed that type 12 was involved in more than 90 per cent of their cases of nephritis

We know that infection plays a role in some forms of allergy, but we are uncertain of the nature of that role Nephritis is then a condition in which the immunological response to a certain specific type of streptococcus seems to be involved. Looking back over the long period in which efforts were made to prove the role of the streptococcus serves to emphasize how very confusing such specificity can be when the bacteria with which we work are so often only incompletely characterized.

We have very little knowledge of bacteria in their relationship to the family For instance, although we know that after a streptococcal sore throat the organism can be cultured for weeks or several months, we do not know how long it may last within a family group We have even less knowledge of many other bacteria including such prevalent organisms as the haemolytic staphylococci. If families can carry certain flora as a group or if chronically infected carriers in a family can act as a source of organisms, then differentiation between infection and heredity may become very difficult Little can be done about heredity in our present state of knowledge, but disease is another matter, so the findings of Rammelkamp should stimulate efforts to understand the real role of infection in allergy

The part that bacteria (or virus) might play could be of different sorts They might act as adjuvants to sensitization, or they could be antigens themselves. They could simply act as agents causing specific localization of antibody in the shock organ There are many examples of all of these activities. For instance, Burkey (61) discovered that he could produce ragweed allergy in rabbits with doses that normally would not sensitize if he gave staphylococcus toxin at the same time Sensitivity to specific organisms is too well known to require further comment. The role that infection might play

connective tissue. In the experimentally induced allergy in animals given large doses of horse serum or almost any protein, severe vascular changes, fibrinoid in character, are produced in a large percentage of animals It was on such observations, with effects based upon a known cause, that Klinge (68), Rich (70), and many others accepted the idea that fibrinoid changes of the connective tissue indicated hypersensitivity.

The question, that may be properly asked, is—are these changes specific and can there be no other conclusion than that changes in intermediate substance must be allergy? Klemperer (66) and his associates demurred at this sweeping acceptance because:

> first, our clinical observations had not revealed any of the conventional symptoms and laboratory findings of hypersensitivity, second, we were aware that local fibrinoid connective tissue change was frequently observed in situations in which allergy could definitely be ruled out and well-defined other causative factors be found such as enzyme action, etc. But beyond these reasons we felt that to accept the allergic hypothesis meant only to explain an obscure structural alteration by an equally obscure pathogenetic mechanism.

At this time, interest returned to the hematoxylin bodies as a diagnostic criterion, and in 1950 Klemperer *et al.* (71) reported these lesions in 32 of 35 cases and later Gueft & Laufer (72) in all of 17 consecutive cases.

About this time Hargraves *et al* (73) independently reported the discovery of the lupus erythematosus cell in the bone marrow of patients with systemic lupus. A year later the "L.E" cells were found in the circulating blood by Sundberg & Lick (74). These cells until recently had not been found in any other so-called collagen disease; hence these appeared to be a pathognomonic sign of lupus of great clinical value. Cytochemical studies disclosed the hematoxylin bodies as a protein derivative, and the same method of study applied to the "L E" cells of the bone marrow led to the conclusion that they were identical optically and chemically with the hematoxylin bodies (75). Haserick & Bortz (76) and Hargraves (77) then showed that the plasma of patients with lupus will produce the characteristic lupus erythematosus cells *in vitro* from normal cells of bone marrow Further, Haserick *et al* (78, 79) determined that this property of plasma lay in the electrophoretically separated gamma globulin of the blood of patients with acute lupus. Such globulin injected in rabbits developed a specific antibody which prevented the *in vitro* lupus erythematosus plasma phenomenon.

While further studies are needed and are going on, the present feeling is, in the words of Klemperer (66), that "it is suggestive that the fibrinoid in lupus specifically consists of the breakdown products of nucleo-proteins, while fibrinoid in other diseases is a different protein " From further studies on this subject it appears from the work of Kurnick *et al* (80) that the lupus erythematosus plasma factor acts to inactivate a desoxyribonuclease inhibitor that is present normally in polynuclear leucocytes as reported by Henstell *et al* (81). To quote Klemperer (66) "the lupus erythematosus factor

stance. It acts only in conjunction with complement and magnesium and "participates in such diverse activities as the destruction of bacteria, the neutralization of viruses and the lysis of certain red cells." Human properdin is an euglobulin. It does not appear to vary greatly in quantity from person to person. The author and his colleagues have already done a great deal of work towards identifying it as a separate entity with respect to other known active components of the blood. They have also measured its presence in several species. A finding of considerable interest is that the rat, which is highly resistant to infection, has the highest titer of any species tested, and the guinea pig, whose resistance is notoriously low, has the lowest. The other animals tested and human beings fall in the order of their natural resistance to disease. No doubt by the time of the next annual review much more will be known about these nonspecific substances and their relationship to immunity.

IMMUNOLOGICAL ASPECTS OF CERTAIN DISEASES

Disseminated Lupus Erythematosus

Although the term lupus erythematosus dates back to 1850 with Cazenave's use of the term for the chronic cutaneous lesions described by Wilan in 1809, it was Kaposi who adopted the term for the acute systemic disease which he believed was basically the same as the chronic discoid form, a relationship not yet fully proven.

Continuing studies showed that the conspicuous pathologic feature was a fibrinoid degeneration of collagen fibers and alteration of the homogenous ground substance, and as Klemperer (66) states "the conclusion was reached that systemic lupus erythematosus was defined anatomically by a systemic alteration of the connective tissue, especially of its extracellular components." Since similar pathologic changes were observed in scleroderma and in rheumatic fever, the term diffuse collagen disease was used by Klemperer *et al.* (67) without meaning to imply an identity of pathogenesis but merely calling attention to the widespread alteration of connective tissue in various and apparently unrelated diseases

It is necessary to justify a discussion of lupus in any review of subjects pertaining to allergy and this is found in the work of Klinge (68) who had called attention earlier to the general connective tissue alterations in acute rheumatic fever as well as rheumatoid arthritis, alteration which included both fibrinoid degeneration of collagen and changes in the ground substance. He, first, and then others (69, 70) following him regarded these fibrinoid connective tissue changes as manifestations of hypersensitivity (or allergy). Hence all and sundry diseases with such structural alterations, as scleroderma, dermatomyositis, periarteritis, serum disease, and others, including [illegible] considered to be allergic or at least to have a pathogenesis

Finally, Reinhardt & Waldron (86) and Shackman *et al.* (87) each reported on one patient with symptoms simulating disseminated lupus in whom "L.E." cells were found in the blood.

It would be premature to say that these cases of abnormal reactions to drugs are identical with systemic lupus erythematosus as it spontaneously arises, but it does raise the question whether "L.E." cells can longer be considered pathognomonic of lupus It would also, for instance, be interesting to know if the gamma globulin of these patients with drug reactions would, when injected into rabbits, produce a specific antibody that would prevent the lupus plasma phenomenon. Such cases will give impetus to the study of the cause of lupus, but it should not be assumed without more evidence that their toxic states are identical with acute disseminated lupus erythematous.

The Purpuras

The purpuras constitute a group of diseases of varying symptomatology and of unknown origin if we except the relatively few cases of so-called "allergic" purpuras attributable to foods or drugs Ackroyd (88) in a recent paper gives two clinical classifications of the allergic purpuras. The first classification is purpura associated with erythema, joint and visceral symptoms, the Henoch-Schönlein syndrome "Apart from a very small proportion of cases which are due to foods and are truly allergic, the cause of the condition is unknown and its allergic origin entirely unproved " It seems indicated here to state that even in the cases of foods an allergic mechanism has not yet been shown for rarely do the allergens give immediate wheal-type reactions The proof, in the absence of demonstrable antibody, rests entirely and solely upon clinical trial and error which is notoriously untrustworthy, unless secured under identical conditions as to amount and time interval on three separate trials. The second classification is true purpura, without exanthemmata and caused by infections or drugs. These are dealt with separately as the mechanisms appear to be different

The conventional classification of purpura based on the presence or absence of thrombocytopenia seems no longer to hold or serve a purpose for as Ackroyd (88) states "purpura due to drugs or infections may be either thrombocytopenic or athrombocytopenic, moreover the same drug or infection may produce either type of purpura in different individuals " Abnormal capillary fragility is generally accepted as present in all purpuras for with intact vascular endothelium hemorrhage does not occur But there appears to be no correlation between the extent of hemorrhage and the degree of thrombopenia for Ackroyd cites many reports showing "severe purpura with normal platelet counts"—and the converse "a low platelet count occurring in a patient without hemorrhagic symptoms "

However, the frequent association of purpura and thrombocytopenia required an explanation that was first supplied in a paper by Bedson (89). It is of great historical interest Among various experiments when he reduced the platelet count in guinea pigs with antiplatelet serum, purpura occurred;

penetrates the cell membrane (of leucocytes), reacts with the inhibitor and thus the normally present desoxyribonuclease is free to attack the chromatin."

The most recent work of Gueft & Laufer (72) reported findings which permitted an integration of the two hitherto unconnected histologic criteria of the basic tissue changes in systemic lupus erythematosus, the hematoxylin stained bodies, and the generalized fibrinoid connective tissue damage, and further "the observation here recorded permits a separation of the fibrinoid alterations in systemic lupus from those which occur in other diseases, particularly those associated with necrotizing arteritis"

It will not be amiss here to recall the discussion of the proteolytic activation theory of the allergic and anaphylactic reaction as discussed earlier in this review. It is quite in line with the developing concept that lupus is itself based upon the activity of a protease (desoxyribonuclease) and while it does not establish an identity of the basic phenomena of hypersensitivity and lupus, at least it seems to relate them to the point that both may be pathogenetically based upon a disorder of the enzyme systems.

While these important studies on the mechanism have been going on, there was little advance on the "etiologic front" until the report by Moolten & Clark (82), not yet confirmed, that "they have twice isolated a virus from a patient with systemic lupus erythematosus which was found capable of reproducing the 'L E' cell phenomenon *in vitro* A human volunteer (the patient's husband) injected repeatedly with the formalin-inactivated virus, developed a rising titer of neutralizing antibody This serum inhibited the 'L.E' cell phenomenon when mixed with the patient's serum or virus" Such a finding does not preclude the possibility of sensitization as the ultimate pathogenetic factor in which infection directly or indirectly plays a part.

In addition to this there are four recent publications in which syndromes or findings at least similar to, if not identical with, lupus have been produced by known agents, namely drugs.

Walsh & Zimmerman (83) showed the "L E" phenomenon in three patients, all males, exhibiting penicillin hypersensitivity Dustan *et al.* (84) record the occurrence of untoward symptoms in 13 out of 139 patients under prolonged treatment with hydralazine (Apresoline) In the summary they state "a syndrome supervened, which, in its milder phase, resembled rheumatoid arthritis and, in its severer form, simulated aspects of acute systemic lupus erythematosus" "L E" cells were found in two of the five severe febrile cases The symptoms usually disappeared promptly upon withdrawal of the drug and in eight cases reappeared upon resuming therapy Eight of the 13 patients were males In the next report, Perry & Schroeder (85), likewise implicating hydralazene, state "late reactions to this active chemical agent were predicted, these have taken the form of collagen disease in all stages of severity" In another place they state that "although lupus erythematosus (L.E) cells were found in the blood of only one patient, in two other patients the disease closely simulated disseminated lupus erythematosus"

curs only in presence of complement which is not required for agglutination alone. (*f*) A patch test of Sedormid to the unbroken skin produced a delayed (48 hr.) petechial reaction that was specific for the sensitized patient. This indicates action on the capillaries directly without mediation of platelet.

From these findings the author surmises that a Sedormid-platelet combination acts as antigen to produce anti-platelet auto-antibody. In the *in vitro* system if complement be present, lysis occurs; without complement there is agglutination without lysis Since the same phenomena occur with platelets of normal blood a marked affinity of this drug for platelet is assumed to occur in all patients given the drug, but it must be a compound of low antigenicity as it stimulates the antibody only in those few whose system, for unknown reasons, is tuned to and responds to this stimulation. The platelet antibody must also act to produce capillary damage, but a further suggestion is offered to account for the capillary fragility; namely, that Sedormid may combine with endothelial cells to form antigen which, reacting with antibody, produces the vascular lesion of purpura Whether these findings apply fully to the thrombocytopenia produced by unknown causes or by other drugs is not now known, but agglutination to quinidine and quinine has been shown (90, 91)

Lozner (92) discusses the importance of the spleen in idiopathic thrombocytopenic purpura. There are two schools of thought regarding this. one, that the spleen inhibits the formation of platelets, the other, that platelet destruction is caused by the spleen Neither explanation is satisfactory for they do not account for spontaneous remissions nor the inadequacy of splenectomy. Still more important is the fact that the recent studies "have favored the existence of a humoral substance, probably an antibody in the plasma" Lozner (92) refers to the observations of Epstein *et al* (93) on the occurrence of thrombopenia in infants born of mothers with the disease It occurred in infants regardless of splenectomy in the mothers and in all cases was transient. Lozner credits Evans (94) with being "probably the first to demonstrate the presence of a platelet agglutinating factor" in these idiopathic purpuras This was brought out by Evans who reported on the occasional coexistence of acquired hemolytic anemia and thrombopenic purpura and to the positive anti-human globulin rabbit serum (Coombs) test using platelets instead of erythrocytes in thrombocytopenia of certain patients who were not anemic. This is the first time in which the antiglobulin serum was applied to other than red blood cells

The immunological mechanisms of idiopathic thrombocytopenic purpura have been further advanced by the work of Harrington *et al* (95) who noted the prompt drop in the platelet count of most normal humans after transfusion with blood or plasma from patients with thrombocytopenic purpura; when Stefanani *et al* (98) repeated this experiment by injections of plasma, the normal recipients not only showed a drop in platelet but developed purpura, as well as a change in the megakaryocytes

The experiment of Harrington (95) was reversed by Stefanani *et al.* (96)

for this anti-serum not only reduced platelets but on section the capillary walls showed damaged endothelium. This latter was the important lesion. These early experiments are noteworthy as showing antigenic relationship between capillary endothelium and platelet and by the same token the megakaryocytes from which platelets are derived. Ackroyd (88) further calls attention to the close resemblance of this syndrome of Bedson

> to a condition in man, namely, thrombocytopenic purpura due to hypersensitivity to the drug sedormid (allyl-isopropyl-acetyl-carbamide) in which it has been shown that there exists in the sera of patients who suffer from this form of hypersensitivity an antibody, which in the presence of sedormid, destroys platelets, and also damages the vascular endothelium

While Bedson's facts are undoubtedly correct one must remember the lack of correlation between the amount of bleeding, i e., the degree of capillary fragility, and the lowering of platelets in some patients. Ackroyd explains this away as possibly showing variations in the susceptibility of patient's tissues But it is only an assumption that there may be tissue difference in the various clinical purpuras with different infections and different drugs, in one case a greater susceptibility of the platelet and megakaryocyte (thrombopenia but no purpura) and another, more vascular damage (hemorrhage) with normal platelet count.

Medical literature records many drugs as causes of purpura. These have been well assembled by Ackroyd (88) In some of the recent reports the immunological work has been extensive, notably the report by Ackroyd on sedormid, and by Larson (90) and Hirsch & Dameshek (91) on quinidine These will be discussed under the general heading of pathogenesis to follow.

Pathogenesis—In the typical nonthrombocytopenic purpuras, the Henoch-Schonlein syndrome and the so-called purpura simplex, little or no progress has been made in definitely pinning down the pathogenetic basis or the etiology except for those few cases ascribed to foods or drugs in which even the pressure test for fragility of capillaries is infrequently positive and in which the platelet count is normal or but slightly reduced

In the thrombocytopenic group immunologic studies have contributed findings of great interest We shall review first among recent noteworthy contributions the latest available by Ackroyd (88) who subjected a patient with thrombopenic purpura attributable to Sedormid [(2-(isopropyl-4 pentenoyl)urea] to exhaustive and critical analyses The following points were brought out (*a*) Sedormid caused platelet agglutination and lysis with reduction of platelets by *in vitro* test using the sensitive patient's fluid blood (*b*) *In vitro* coagulation of patient's whole blood with Sedormid shows lysis of platelet during coagulation which occurs in normal time but clot retraction is reduced (*c*) Lysis of platelets by Sedormid reduced complement in the blood of Sedormid-sensitive patients but not in normal blood (*d*) Lysis of platelet is caused by a factor in the sensitive serum It acts identically on platelets of normal or sensitized blood in presence of Sedormid (*e*) Lysis oc-

body formation. Morgan (105, 106) was the first to apply the term allergy to the lesions produced in monkeys injected with emulsions of cord and nervous tissue and adjuvants while about the same time and independently Kabat *et al.* (107, 108) reported the disseminated encephalomyelitis using similar techniques. The lesions and symptoms thus far produced were all acute and disseminated and could be produced in all mammals using adjuvants with brain, cord, or nerve emulsions but no other tissues (109). Ferraro & Cazzulo (110) were able, using small doses of allergen, to create a condition simulating the chronic state. Finally Freund *et al.* (111) with a specially grown mycobacterium were able to produce a chronic encephalomyelitis in which lesions and symptoms closely resembled those of multiple sclerosis It remained for Kabat *et al.* (112) to close the remaining gap and demonstrate autosensitization by the injection of monkeys with emulsions of their own brain in adjuvant They concluded that the antibodies systemically produced eventually passed to the brain and produced perivascular lesions like those found in multiple sclerosis.

But the study has been pursued further, using the techniques found successful in the studies of glomulo-nephritis in which autosensitivity was established Here the kidney lesion was produced by the injection of nephrotoxic antiserum from a sensitive to a normal animal This has been tried by several investigators (105, 111, 113, 114) using brain tissue, but thus far has failed in the hands of all

What about some of the more direct evidences of sensitization as applied in clinical allergy—for example, the skin test? These tests have been done by Kopeloff & Kopeloff (113) and by Lipton & Freund (115) and both have reported them positive in monkeys, only under conditions of heterologous stimulation. The skin test was negative to the homologous antigen, but an injection of brain emulsion did produce the cerebral reaction However, the most recent skin test studies by Waksman & Morrison (116) showed not the immediate urticarial wheal but a positive delayed tuberculin-type reaction which they felt corresponded in activity to the intensity of the encephalomyelitis

In more recent work, Waksman & Adams (117) showed an interesting selective activity of antigen on sensitized cells Rabbits injected with homologous spinal cord antigen later gave responses of peripheral nerve and spinal cord as well as central nervous disease In contrast, the use of homologous sciatic nerve antigen produced lesions of nerve and ganglia while the rest of the nervous system were unaffected The lesions of this experimental allergic neuritis resemble the encephalopathies in pathology, but clinically there is strict localization of symptoms simulating the neuritis or neuronitis of infectious origin

Passive transfer of sensitivity has been tried both with serum and with lymphocytes (by Chase's method) but has not been successful as reported by Kabat *et al.* (118). The explanation they offer is that failure is attributable to antibody fixation by antigen in the donor's nervous tissue This is about where the experimental study stands today and the chain of events that

and Hirsch *et al.* (97) who injected platelet rich blood or platelet suspensions into thrombopenic patients and observed rapid platelet disappearance especially in the acute cases. These observations make clear the reasons for thrombopenia in the new-born babies of thrombopenic mothers originally described by Epstein (93). The further studies of Harrington *et al* (99) indicate that there are platelet types, probably three, roughly corresponding, apparently, to the blood types. They make clear the differences that may exist between autoagglutinins and isoagglutinins

In spite of the excellence of the work being done the entire picture is not yet clear and Harrington (99) sums up the work by saying that

> the evidence suggests that the disease may not be a specific entity, but a syndrome which may develop as a consequence of more than one abnormal mechanism ... In some, a deficiency of a factor or factors necessary for platelet formation; in others, to suppression of platelet production . . . and in others, to excessively rapid platelet destruction.

As matters stand today the end is not yet in sight but the study is in the hands of competent investigators and is well along on the road to a solution of the mechanisms involved. Taking a broad view of the ultimate answer, one might hazard the opinion that, as in lupus, an underlying defect in the enzyme system might be to blame.

Multiple Sclerosis[4]

Among a number of diseases, the etiology of which is still unknown, multiple sclerosis is one that is being carefully studied to determine whether or not allergy might be implicated in the pathogenesis In other words, is there a sensitization factor to some extrinsic or intrinsic agent that accounts for the lesions and therefore the symptoms characteristic of such a disease.

The possibility of allergy as a cause of the disseminated cerebral lesion is not a new idea. It seems to have begun in 1927 with the suggestion by Glanzmann (100) that post-vaccinal encephalitis was a phenomenon of sensitization. There is a recent paper by Hurst (101) who experimented on rabbits in an attempt to explain the paralytic accidents associated with anti-rabic treatment In this study Hurst supports this opinion of Glanzmann as follows "The balance of evidence is in favor of an allergic basis for the post-vaccinal type of encephalitis and for some of the paralytic accidents of anti-rabic therapy in man and in the dog " In 1933 and 1935 Rivers and his associates (102, 103) made observations on monkeys injected with heterologous brain emulsion. Lesions of acute encephalitis with myelin destruction were produced. A shift in the allergen from heterologous to homologous brain tissue was reported by Schwentker & Rivers (104); then followed other experiments using Freund adjuvants in an attempt to enhance the possible anti-

[4] I wish to acknowledge the opportunity afforded me by Dr. Samuel Prigal of reading his extensive and still unpublished monograph on Multiple Sclerosis.

evidence of previous infection was indicated by the antistreptolysin and antistaphylolysin titers.

Although these studies are not conclusive it would seem that investigation on the basis of bacterial infection acting as an adjuvant or as the sensitizing agent might be worthwhile in view of the synergistic effects of bacterial products in the stimulation of sensitization to sluggish antigens as first shown by Burkey (124).

In conclusion it may be said that the experimental work with autosensitization and the production of isoantibodies comes nearer to offering proof of a possible allergic factor in multiple sclerosis than do the clinical observations which are meager and do not as yet afford any substantiating evidence for allergy The work, however, should be continued for sooner or later the pathogenesis as well as the cause must be found.

IMMUNOLOGICAL RESPONSES IN HOMOGRAFTING

In February, 1954, there was a two day conference in New York City on "The Relation of Immunology to Tissue Homotransplantation" under the auspices of the New York Academy of Sciences, Section of Biology. The purpose of this was to discuss the extensive immunological studies that are underway here and abroad The incentive for this work is that tissue homografting as done now and in the past is completely unsatisfactory. In fact, the surgeons of today admit to the almost universal failure of tissue homografting. An explanation for this is now actively being sought largely on the basis that sloughing of the graft is induced by an immunological reaction by the host against the graft of skin of the same species On the other hand, autografting, i e , from one area to another part of the same body, is highly successful, as is the grafting from one monozygous twin to another which is an autograft

One of the papers by Cooke (125a) discussed the evidences for development of hypersensitivity in the host, but this is not meant to imply that the tissue incompatibility resulting in the slough of the graft is necessarily attributable to allergy If allergy be present it might be a result rather than a cause

The facts indicating allergy are these (*a*) Every homograft appears to live, and blood vessels start to grow, but after an average of 10 days evidences of slough begin at the edges of the graft This is about the time necessary for the development of antibody whether it be of the immediate wheal type or the delayed tuberculin type allergy It is still a moot question as to what type of antibody it could be, a precipitin, lysin, agglutin, or skin sensitizing (nonprecipitating) antibody or how it might be determined Studies thus far have failed to show any specific antibody for the homograft which is to be considered as a foreign protein If a primary graft is sloughed because of local (or general) sensitivity, then on the principle of Von Pirquet's accelerated reaction, a second identical graft should begin to die much earlier, by the second or third day This is what Medawar (126) has found in the rabbit experiments In man, second set grafts are not satisfactory largely as a result of

would establish proof of allergy as the factor in demyelination as exhibited in multiple sclerosis is by no means complete.

There are reasons for hesitation in the acceptance of sensitization as the answer to the cause of multiple sclerosis One is that no evidence has yet been produced that an individual can directly become sensitive to his own living tissues, the so-called "horror intoxicus." Again there are other processes that will produce demyelination, e.g , anoxemia and various drugs such as barbiturates, lipolytic enzymes, and venule thromboses, infections (bacterial or viral), and hormonal and metabolic disorders. As Hurst (101) puts it: "Surveying the whole field of demyelinating diseases of man and animals it seems quite inconceivable that there can be a common basis for all."

Kennedy (119) was first of the competent clinicians and recognized neurologists who in 1936 contended that many patients with early symptoms of what had been diagnosed as multiple sclerosis were in reality allergic encephalopathies. One of us (RAC) had the opportunity of carrying out an allergic survey on a number of his patients. An important basis for his thesis was the familial background or personal history of accepted allergy. In no case could a positive diagnosis be made of a sensitization to any inhalant or food factor that could conceivably be related to the neurological lesion. The only possible explanation lay in the assumption of a bacterial allergy, and this is a diagnosis usually arrived at by exclusion of other causes and one for which positive proof is rarely established

Jonez (120) is perhaps the major exponent of an allergic factor in multiple sclerosis, but his data are much too sketchy to be acceptable, and the results of therapy on the basis of allergy are inconclusive when one considers the variability in the course of multiple sclerosis as well as the uncertainties of diagnosis, especially in the early stages Ehrentheil (121) *et al* have recently presented a paper on the "*Role of Food Allergy in Multiple Sclerosis*" These authors depended upon the ophthalmic rather than the cutaneous test on the ground that it was more reliable. The results with these two types of tests showed little correlation, with an incidence of positive ophthalmic reactions to an extract of rye as high as 77 8 per cent However, with 69 per cent positive in the control group, it would indicate an irritative rather than an allergic response. Using the trial and error method of feeding and withdrawing foods to which the patient reacted, the results were inconclusive in that the patients were not under supervision and the tests were not carried on for a sufficient length of time It would be a mistake to accept these data without confirmation from several sources

The influence of infections either viral or bacterial has received some attention Mention has already been made of the use of vaccine virus by Rivers as an adjuvant, and more recently Jervis & Koprowski (122) used rabies virus in the production of encephalitis in mice Stortebecker (123) has discussed staphylococcal and streptococcal infections as playing a part on the basis of history of such infections preceding the onset of multiple sclerosis, and the

immunological response, (*b*) that the antigenic properties of a tolerated graft continues in being, and (*c*) that lymph nodes are one of the anatomical instruments of the host's reaction against homografts.

Pressman's presentation on "Tissue Localizing Antibodies" (125d) dealt with a subject that is of vital significance to an appreciation of the localized clinical manifestations seen in many of the spontaneous allergies of man. In regard to tissue transplantation, Pressman suggests that "there may be formed antibodies cytotoxic to the transplant," and "antibodies capable of damaging the host's own tissue In any case an antibody must localize in a particular tissue for it to be cytotoxic for that tissue " Certain heterologously formed tissue antibodies were iodinated with radioactive iodine. When injected into the tissue donor-animal, these antibodies could be traced to the tissue for which they were specific. In certain instances "the localizing antibodies closely paralleled the properties of the cytotoxic activity "

These papers have been quoted at considerable length because they illustrate not only the excellence of the immunological work that is in progress in a field of increasing importance but also for the implications that such basic work carries for immunology in general and ultimately for some of the human diseases, especially those of unknown pathogenesis

PULMONARY FUNCTION

Several recent studies on pulmonary function attest to the increasing interest in the subject for clinicians as well as physiologists The objective of all is to secure information on first, pulmonary ventilation, and second, gaseous exchange, the two essential divisions of pulmonary function

According to Schiller & Lowell (130)

> Tests of pulmonary function may be classified as follows 1 Measurement of lung volume and its subdivisions, 2 tests of breathing capacity, timed vital capacity and maximum breathing capacity, 3 the distribution and "mixing" of the respired gas in the lung, 4 the arterial blood gases, 5 tests of over-all pulmonary function such as the volume of oxygen removed per liter of air breathed and the saturation rate

It is obvious that the accuracy of many of these tests depends on circulatory efficiency, the severity of the disease, training and co-operation of the patient, and the element of fatigue; also the margin of error in duplicating the tests is very high Comroe (131) states that "because of the variation in valves, tubing, and spirometers, it is impossible to compare very closely the data obtained in different laboratories "

It is clear then that while an exhaustive study of lung function may be necessary for the evaluation of risk in cases where lung surgery is contemplated, many are too elaborate and technically complicated and not necessary to the clinician A few basic tests will act as diagnostic and prognostic aids and permit one to follow the course of the disease (132, 133).

The clinician interested in allergic disease of the lower respiratory tract

technical difficulty encountered at the site Hence this point cannot be settled now in the human.

(*b*) Eosinophilia is generally regarded as evidence of allergy. Brown & McDowell (127) reported many eosinophils in the sloughing graft of a patient. The same findings are reported in animals, and McNichol (128) recorded a blood eosinophilia in a child. The most complete report to date is that of Rogers *et al.* (129). They found an eosinophilia in both blood and tissue in 10 consecutive cases. It subsides to "normal" levels as the last vestiges of the homografts dermal pad sloughs away." It does not occur in autografts from self or identical twins, thus indicating that such tissues are not foreign protein

(*c*) The tissue change at a homograft site consists of a rather sudden conclusion, that is, thrombosis or necrosis of the new vessels supplying the graft This suggests an Arthus type lesion which admittedly is not common in man. It is the analogy of the anaphylactic type of sensitization in which the only cells directly affected by the antigen-antibody reaction are involuntary muscle and vascular endothelium. The graft necrosis results as circulation is interfered with by exudate in tissue spaces and damage to vessel walls

That an allergic response occurs at the graft site appears to be indicated but as yet there is no proof that it acts as a causative factor in the skin slough, and this cannot be done until the mechanism can be shown more conclusively, directly or indirectly.

Another paper presented at the conference was by Hardin & Werder (125b). An antigen of skin was injected in varying amounts into mice in order to "paralyze" the immune response of host animals receiving homologous skin grafts Over 50 per cent of the grafts permanently survived. This would indicate the ingenious and successful use of prolonged desensitization and by the same token implies that the homologous skin graft acts as a sensitizing antigen

The studies by Billingham *et al* (125c) on "Acquired Tolerance of Tissue Homografts" were of great interest in showing "an induced state of specific non-reactivity to a substance normally antigenic." We quote from the prepublication abstract of their paper as follows·

> Tolerance of homografts can be brought about by exposing a mouse or chicken embryo to tissue antigens in the epoch of development before it is capable of immunological response If, for example, a CBA mouse in the 16th–17th day of foetal life is inoculated with tissue cells from an adult A-line donor, it fails to develop the capacity to react against A-line tissue homografts transplanted to it later in life Tolerance is specific, for the tolerant CBA mouse does not lose its capacity to react against homografts from a mouse belonging to a different strain, e g , AU

Further experiments showed that this tolerance could be abolished by grafting regional lymph nodes of a normal CBA mouse into the tolerant CBA host. The authors state that the results of their experiments give grounds for believing, (*a*) that tolerance is attributable to a primary failure of the host's

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really needs a few simple recordings that will help to differentiate and evaluate the disability resulting from asthma, emphysema, interstitial fibrosis, and parenchymal involvement. Most patients with chronic dyspnea will eventually come under his care and, since most of these are ambulatory, the tests should be such that they may be frequently carried out and compared with normal values as given by Myers (134) or Baldwin *et al.* (135).

All authors seem to agree that vital capacity as recorded by the simple spirometer has practical value of determining ventilatory capacity but without regard to lung efficiency. Its value is enchanced by a tracing of the patient's breathing combined with time recording. Such studies were recorded by Bachman *et al.* (136). They noted the delay in expiration time in all asthmatics, as every clinician would expect, as well as its shortening after inhalation of a nebulized epinephrine-type drug. This indicates the degree of reversible bronchial obstruction as found in pure asthma, especially in young adults. Delayed expiration after inhalation of bronchodilators would indicate possible permanent bronchial obstruction, or lessening of lung elasticity as in emphysema, fibrosis, or extensive parenchymal diseases.

A recent paper by Cobb *et al* (137) compared the radiographic chest volume (RCV) as determined on routine postero-anterior and lateral films, taken at the end of full inspiration, with the total lung capacities obtained by spirometry and an open circuit method of estimating functional residual capacity. They state that

> the closeness of correlation between radiological and gaseous methods of lung capacity determination in the group possessing volumetrically intact pulmonary tissue was sufficient to suggest its soundness and feasibility in screening large numbers of individuals for abnormal changes in pulmonary compartment ratios by a combination of simple spirometry and radiological measurements of routine chest x-rays.

It correlated best in patients with emphysema etc., but was poor in disease with mass replacement of ventilating parenchyma This relatively easy procedure would be a boon to the clinician in determining the amount of residual air in proportion to the vital capacity obtained by simple spirometer or with time recorded tracings of breathing before and after the relief of bronchial constriction by means of injected or inspired epinephrine-type drugs In this way the reversible and so-called irreversible pulmonary changes could be followed from time to time. This would afford the clinician a new insight into the progress, beneficial or otherwise, of the disease and the efficiency of treatment

Most of the students of respiratory physiology stress the rather intricate procedure of the study of gas exchange For the clinician the estimation of pulmonary efficiency as determined by gaseous exchange is not practical until and unless simple techniques are developed There is such a possibility in the future through the use of an improved oximeter to record the oxygen saturation of the blood by a spectrophotometer. Alexander & Reydman (138) have published their observations, and a paper by Franklin & Lowell (139) on the use of this meter is about to be published.

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NEOPLASTIC DISEASES (CANCER)[1]

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Introduction

The original purpose of these *Annual Reviews* was to furnish a critical analysis of the current and recent literature in a given field Yet not every aspect can be scrutinized in detail, nor every paper receive individual mention. Indeed, the mere abundance of data would effectively prevent it, and in itself presents a growing problem, towards which there are two extreme types of reaction. first, that of the happy researcher who is content to ignore the original literature, and to rely upon others for his information; and secondly, the reaction of those whom the literature totally enslaves The more philosophic approach is the middle way, allowing a conspectus of essential detail without obscuring general trends, or hindering the synthesis towards which we travel. Suggestions for the rationalisation of the literature have been put forward in the field of cancer research by Kennaway, and for science generally by Bernal, among others Yet the wind bloweth where it listeth. Perhaps the present system—or the lack of it—mirrors both the face of nature and the unpredictability of research, and is not to be improved by undue organization Our best hope must still lie in unrestricted freedom and variety of publication, while minimizing the attendant difficulties, unquestionably real, through periodic assessments of the kind which the *Annual Reviews* afford

General Works

The interval under review has seen the publication of numerous works of great general interest, among which may perhaps be mentioned a second edition of Willis's classic on *The Spread of Tumours in the Human Body* (1), of his *Pathology of Tumours* (2), and of Greenstein's *Biochemistry of Cancer* (3), a revised edition of Woglom's translation of Oberling's *The Riddle of Cancer* (4), and a new book by Oberling in the series *L'Avenir de la Science* (5) Homburger & Fishman's *Physiopathology of Cancer* (6), even though it is not easy to digest, will be valued as a massive compendium Cameron's *Pathology of the Cell* (7) shows a wide sweep, and should be read especially for its accounts of the cell theory and of the biology of transplantation and regeneration A fresh venture is *Advances in Cancer Research* (8), containing authoritative accounts of specialized aspects, notably in relation to carcinogenesis, not only by well-known names but by the new generation. Useful symposia on fundamental cancer research, and on nutritional factors, have been published in the *Texas Reports on Biology and Medicine* (9, 10).

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region, which appears to be an essential feature of the carcinogenic molecule, (29 to 36). An independent, critical appraisal and reinvestigation of the French thesis has been provided by Coulson (37) in a form eminently readable even by the general scientist. In the meantime Pullman has extended and modified the earlier conception in such a way as takes count of other molecular features, and promises to yield a true picture of the properties essential for carcinogenic action (38). Such considerations do not, of course, in any way indicate the nature of the biological receptor towards which the special reactivity properties of the carcinogen are directed or with which it combines. For this purpose other methods must be used, as in the studies by Heidelberger and his group of the interaction of labelled carcinogenic hydrocarbons with tissue constituents (39), and in particular of the structure of protein-bound compounds which may be isolated following the topical application of radio-dibenzanthracene (40) These compounds recall the similar substances described by Miller (41) as produced in the course of azo-dye carcinogenesis (see below), and this author has himself studied the formation of protein-bound derivatives of 3,4-benzpyrene in the epidermal fraction of mouse skin. The same and related carcinogens also form complexes with purines and nucleic acids, a phenomenon which has been investigated by Boyland and others (42, 43) and which may be significant in the biological reaction

When individual carcinogens are applied simultaneously, their action may either summate or exhibit mutual interference, in the latter case suggesting some kind of competition for the hypothetical receptor. Recent examples include an antagonism between 2-aminochrysene and methylcholanthrene (44), between 2-acetylaminofluorene and 1,2,5,6-dibenzfluorene (45), and an inhibiting influence of methylcholanthrene on the induction of hepatic cancer by 3′-methyl-4-dimethylaminoazo-benzene (46) (see also 47, 48).

Biochemical and histological studies of the action of carcinogens on the skin include accounts of the appearance, metabolism, and disappearance of 3,4-benzpyrene in the epithelium of mouse skin after a single application (49), of the significance of the mouse hair cycle in epidermal carcinogenesis (50, 51), and of mitotic activity in relation to carcinogenesis in the rabbit skin (52).

The possibility was suggested by Cook over 20 years ago that abnormalities of steroid metabolism, of a kind which might readily occur under certain pathological conditions, would lead to the formation in the tissues of traces of potent carcinogenic hydrocarbons such as methylcholanthrene, and so conceivably account for the occurrence of cancer "spontaneously" Although no direct evidence has so far been adduced, the feasibility of some such reaction must always be borne in mind and three papers have appeared which are of special interest in this connection, namely, one by Inhoffen on the relationship of the natural steroids to carcinogenic aromatic compounds (53) and those by Fieser (54), and Bloch (55) on various aspects of the chemistry and biochemistry of cholesterol and of its biological synthesis.

Carcinogenesis

In the innumerable approaches to the cancer problem, that of the study of carcinogenesis occupies a central place. It may well be that effective prevention and control will only be possible on the basis of a precise understanding of (*a*) the biological nature of malignant change and (*b*) its expression in chemical terms.

A short but excellent general account, particularly useful for the nonspecialist, is provided by Wolf (11), while the principles underlying chemical carcinogenesis, so far as they are known, have been discussed by Truhaut (12), Druckrey (13), and Buu-Hoi (14), among others. An interesting paper by Nordling (15) submits a new theory on the cancer-inducing mechanism, according to which cancer mortality rises with age by the seventh power. It has been followed by a study by Armitage & Doll (16) of the age distribution of cancer, also in relation to a multi-stage theory of carcinogenesis Further papers have appeared in the series by Iversen & Arley (17, 18), in which an endeavour is made to apply a quantum hit theory to tumour induction. Ingenious as many such approaches undoubtedly are, it is obvious that their value wholly depends upon the extent to which they are verifiable in practice, or stimulate fresh experiment. Along lines similar to those earlier suggested by Rondoni, Ambrose (19) has set forth various entropy considerations in relation to carcinogenesis, and the principle of minimum entropy production in biological systems generally has been further dealt with by Spanner (20).

The writer is naturally intrigued by the similarity of the conclusions gradually being approached by his own group (21) to the opinion of the Millers and the Madison school (22). The former have found that the essential change in malignancy, at least in the case of the biological alkylating agents referred to in detail later, may be a modification by genetic loss, whereas the latter group on altogether different evidence, conclude that the experimental production of liver cancer may be brought about through the gradual deletion of key proteins essential for the control of growth (22) The implications of such a conclusion are briefly discussed below Two major contributions, by Furth (23) and by Hauschka & Levan (24, 25), have greatly illuminated our knowledge of the progressive changes which may occur in the cancer cell itself, as it proceeds from conditioned to autonomous growth, or from greater to lesser biological specificity

Carcinogenic Hydrocarbons—The interdependence of chemical constitution and carcinogenic activity has been discussed by Badger (26) and by Druckrey (27) To the former author we also owe a major work on the structure and reactions of the aromatic compounds (28) Recent years have seen an outstanding contribution by the French school of theoretical physics, especially the Daudels and the Pullmans, through the application of wave mechanics to the study of the action of cancer-producing substances, in particular, the development of a relation between such action and the "activating energy" of chemical additive reactions in the so-called "K"

not be the viewpoint of many others, as for example Truhaut, who has endeavoured to define the principles underlying the use of alimentary colouring matters in a report to an expert committee of the adherent nations of the Brussels Pact (72).

Carcinogenic Amines, with special reference to Cancer of the Bladder.— Numerous papers continue to explore the carcinogenic properties of 2-acetylaminofluorene (73, 74), and of the N-monomethyl and -dimethyl derivatives of 2-aminofluorene (75), and a specially interesting note records the rapid production of malignant hepatomas by simultaneous administration of acetylaminofluorene and tannic acid (76) The carcinogenic action of the aminostilbene series, described by the writer and his colleagues some years ago, has been further studied by Elson with reference to the variations in the expression of carcinogenic action which are imposed by high-protein and low-protein diets (77) In what is in some ways an extension of the earlier aminostilbene work, Walpole and others have been successful in demonstrating the carcinogenic action of 4-aminodiphenyl and its 3,2'-dimethyl derivative (78) The carcinogenicity of acetylaminodiphenyl is mentioned by Sandin and others (79), although it had not been detected by Rudali & Royer (80)

Recent work on the carcinogenic amines has largely centered round the occupational incidence of cancer of the bladder In England, a scheme of research inaugurated by the Association of British Chemical Manufacturers has involved a survey of tumours of the urinary bladder in workmen engaged in the manufacture and use of dyestuff intermediates in the British chemical industry, including the rubber industry, and has led to the official prescription of the disease for purposes of national insurance (81, 82, 83) In association with the same scheme, Bonser and others have carried out an experimental investigation of bladder cancer and have been able to demonstrate, by a technique described by Jull, the direct carcinogenic action upon the mouse bladder mucosa of the β-naphthylamine metabolite 2-amino-1-naphthol (84, 85) Arising from the last observation, Clayson has developed a working hypothesis for the mode of action of carcinogenic amines, based upon the potential carcinogenicity of *o*-aminophenols more generally While the hypothesis still requires further test, it is clear that other factors, and especially the method of excretion of such metabolites, may greatly modify their action (86) Important recent observations are the induction of tumours of the bladder in dogs after injection of 2-acetylaminofluorene and of 4-aminodiphenyl (87, 88)

Carcinogenic Alkylating Agents—Considerable advances have taken place in the past few years through the discovery of carcinogenic properties in various nitrogen mustards and related substances such as the diepoxides, polyethyleneimines and dimethane sulphonyloxyalkanes, and recognition of the fact that these compounds almost certainly act through a process of biological alkylation (89) As a result we may claim to have at any rate glimpsed, for the first time, the likely mechanism of action of one kind of

Azo Dyestuffs.—Reference has already been made to the important contributions of the Madison school, especially the study of those combinations which take place between the tumour-inducing azo dyestuffs and tissue constituents *in vivo*, and their possible role in carcinogenesis (56, 57). A long series of papers includes such topics as the synthesis of "butter yellow" labelled with carbon-14 in the benzene rings (58), and the metabolism of methylated amino azo dyes (59), and the main results of the research have been summarized by the Millers in a notable review (22) and in their *Die Biochemie der Krebsentstehung in der Leber* (60). The resultant hypothesis, namely, that induction of malignant change may occur through the gradual elimination of specific proteins essential for the normal regulation of growth, raises the question (as in the case of the postulated genetic loss brought about by the alkylating carcinogens (below)) of the chemical or enzymatic nature of the proteins so deleted. In general, the oxidative enzyme systems appear to be relatively deficient in induced liver tumours as compared to normal liver (although the activity of lactic acid dehydrogenase is normal); on the other hand, the levels of certain phosphatases, nucleic acid depolymerases, cathepsins, desamidases, and nucleic acid desaminases, are usually about as high in liver tumours as in the normal organ.

The chemical constitution and biological activity of the azo carcinogens have been compared by Badger & Lewis (61), and Weiler describes the changes of serological specificity occurring in the liver during carcinogenesis by butter yellow (62) The synergistic action of mixtures of certain hepatic carcinogens has been described by the Madison workers, and Griffin and others record the inhibition of azo dye carcinogenesis by nitrogen mustard [illegible]

Carcinogenesis by the azo dyes and related substances presents special problems of a practical kind, on account of the widespread use of many such substances as colouring additives to food Nelson & Hagen have described the production of fibrosarcomas in rats injected with brilliant blue FCF, light green SF yellow, and fast green FCF, although there was no reaction with other dyes including guinea green B, amaranth, erythrosine and tartrazine (68) Officially, the toxicological aspect of food colours is being studied by a Preservatives Sub-committee, Secretariat of the Food Standards and Hygiene Division of the British Ministry of Food, while in Germany various reports and recommendations have been issued by the Kommission zur Bearbeitung des Lebensmittelfarbstoffproblems of the Deutsche Forschungsgemeinschaft (69, 70, 71). It is the writer's private opinion, in view of the virtual impracticability of adequate test of the host of substances involved and the impossibility of determining their toxicological effects in man with any precision, that the use of all such artificial and unnecessary additions would best be discarded This is perhaps not regarded as a constructive argument under modern conditions, and would certainly

ties of numerous chemical agents already known, in the field of textile technology, to possess cross-linking properties. At once it emerged that a series of cross-linking diepoxides was capable of producing biological effects largely indistinguishable from those of the mustards (89). Independently, the chemistry of the diepoxides had been intensively investigated in the laboratories of Canadian Industries Limited, Montreal, Canada, and this, with a consideration of the cross-linkage hypothesis, led Hendry and others to a study of their cytotoxic activity, with reference to a suggestion by Rose that these substances might produce their effects, not essentially as individual molecules, but rather as multireacting polymers (95) As a further example of cytotoxic activity of the nitrogen mustard type in a chemical class already in industrial use as cross-linking agents, Hendry, Rose & Walpole described similar properties in a series of methylolamides (96). Yet another example developed from work which had been carried out by the I.G. Hoechst Farbwerke and other groups in Germany during the late war, on the application of polyfunctional agents to the treatment of rayon. Prominent among these agents was the compound triethylenemelamine, now known as TEM in its clinical use (see below), representative of a large class of polyethyleneimines with cross-linking ability and the capacity to effect a great reduction in the swelling properties of both artificial and natural fibres These German developments unquestionably played a large part, which has not been sufficiently acknowledged, in directing the attention of several groups of workers to the polyethyleneimines as cross-linking agents likely to manifest cytotoxic action. Lastly, as the outcome of a deliberate synthetic programme intended to yield new types of bifunctional agents with cytostatic properties, Haddow & Timmis detected biological activity including carcinogenesis in various members of a series bearing sulphonic acid ester groups; namely, the $\alpha\omega$-dimethanesulphonyloxyalkanes, of which one, myleran, (1,4-dimethane sulphonyloxybutane) has proved of some service, on account of its relatively preferential action on cells of the myeloid series, in the treatment of chronic myelogenous leukaemia (97, and see below).

Whatever the precise chemical mechanism of the action of the alkylating carcinogens, it is highly likely that they combine with genetically determinant material, or its precursors. An older view, put forward by the writer 20 years ago, depicted the primary step in chemical carcinogenesis as a characteristic but then unspecified inhibition of the normal growth mechanism, leading to the adaptive formation of a new cell variant, released from the inhibitory influence of the agent which provoked it The newer interpretation suggests that the essential step may be the inhibition of certain fundamental processes of genetic synthesis, followed by the generation of a new self-duplicating fibre or template (chemically, and hence genetically, modified) in a kind of permanent re-orientation of genetic characters, under the impress of chemical reaction by the carcinogen with the initial self-duplicating unit. An important additional concept has also emerged, namely,

chemical carcinogen at least. The discovery of carcinogenic activity in this new class, in substances of relatively high reactivity, simple in structure, and yet possessing molecular features highly suggestive as to their mechanism, has led to speedy progress and to a theory of action which has in turn stimulated many later developments. Whether the proposed mechanism is applicable to other carcinogens remains, of course, an open question, yet note must be taken of the astonishing general similarity of many of the biological effects of the alkylating agents (for example, on the bone marrow, gonads, and in their mutagenicity and carcinogenicity) and those produced by ionising radiations. This parallelism justifies the description of these compounds as radiomimetic, even though there are undoubted differences in the details of their action The investigations in this field by the writer and his colleagues served once more to direct attention to the nucleus as the possible primary site of carcinogenic action even though, in agreement with Ludford (90), it appears that cells can undergo neoplastic transformation without any alteration of nuclear structure that can be detected by the present methods of microscopy.

In efforts to establish the optimal requirements for biological activity in the mustards, it became clear that this is associated with the haloalkyl side-chains exclusively, of which two at least are necessary. Seeking the explanation of this bifunctional or polyfunctional requirement, Goldacre, Loveless & Ross suggested that the two groups might be needed to permit the molecule to react at two different points, lying either on a single surface or fibre, or on two contiguous fibres (91) Of the various possibilities, cross-linkage between the constituent macromolecular fibres of the chromosome itself was of particular interest when considered in the light of the growing assumption that reaction of the mustard carcinogens might well take place directly with genetic material Nevertheless, the cross-linkage hypothesis, which was first suggested as perhaps the simplest interpretation of the facts then available, is now known to be unduly simple In the first place, it is exceptionally refractory to test Secondly, other possibilities are known to be equally likely, as, for example, combination with a precursor or substrate rather than with a genetic determiner directly. Lastly, in actual experience little direct evidence of cross-linkage has so far been obtained. From the extensive work of Butler on the reaction between nitrogen mustards and nucleic acid, it would indeed appear that the effect of the agent may be depolymerizing rather than polymerizing, since deoxyribonucleic acid solutions so treated are degraded, losing their intrinsic viscosity, and breaking down to molecular weights which are markedly less than those of the original material, (92, 93, 94) Nevertheless, the working hypothesis itself remains an endeavour to explain the polyfunctional requirement for the action of the nitrogen mustards *in vivo*, and there can be no doubt of the powerful stimulus which it has exerted, or of the value of the new findings which have come about as the direct result

Among these, the first was the stimulus to examine the biological proper-

could result in the uncontrolled synthesis of such substances, and so to unimpeded growth. Such an interpretation is of course by no means novel, and reference has already been made to the similar conclusion independently reached by the Millers. Also, it may have a vital connection with the absence or slow appearance during embryological development of the oxidative and catabolic enzymes concerned in the transformation of the purines, as a feature characteristic of active growth and synthesis. It is obvious that the possible role of enzyme deletion in carcinogenesis carries implications as to the means by which the process might ultimately be controlled; namely, by a kind of enzyme substitution. That such a possibility is not wholly theoretical is shown by various known examples of such substitution, which have been summarised by the writer elsewhere (89). It has also been possible to demonstrate more recently (unpublished) an inhibiting action of xanthine oxidase on the growth of breast cancer in mice, although the exact basis of the effect is not as yet established Clearly the above views, that the action of certain carcinogens may be a fairly direct one on the gene, and that tumour production may be due to resultant modification or elimination of the gene- or enzyme-mediated regulation of synthesis essential for cell division and growth, permit us to envisage yet a further stage in the chemical or enzymatic means of reversal and control

Carcinogenic Action of Ionizing Radiations—Always of great interest in its own right, the induction of tumours by ionizing radiations has acquired enhanced importance, first in relation to the carcinogenicity of radiomimetic chemical substances (above), and second, because of the increase in radiation hazards, whether real or potential, in peace or in war. The general topic of ionizing radiations and cancer has been discussed by Brues (107) and the histopathology of radiation carcinogenesis by Furth & Upton (108), while the initiation and development of cellular damage by ionizing radiation was the subject of L. H. Gray's Silvanus Thompson Memorial Lecture to the British Institute of Radiology (109) Tumour production by thorotrast was the theme of a special discussion at the International Radiological Congress in Copenhagen in 1953.

In experimental pathology, descriptions have appeared of many tumour types elicited by ionizing radiation the pituitary gland in mice (110, 111), hepatic tumours in CBA mice with colloidal radio-gold (112), tumours in rats following whole body radiation (113), and lymphoid tumors in non-irradiated thymic grafts in thymectomized irradiated mice (114) The latent carcinogenic action of beta-irradiation on mouse epidermis has been discussed by Shubik *et al.*, and the incidence and types of neoplasms in x-irradiated rats following protection by post-irradiation parabiosis by Finerty (115, 116) A strange case, so far unique of its kind but possibly an omen, is the occurrence of osteogenic sarcoma in a muskrat from an area of high environmental radiostrontium (117). The general question of radiation-induced sarcoma has been discussed by Jones (118), and individual tumours reported include a solitary plasmacytoma in a mesothorium worker, and

that the initial combination of the carcinogen with genetic material probably occurs in the resting stage between successive mitoses (98), at a time when, in certain plant material at least, deoxyribonucleic acid synthesis appears to be at a maximum (99). Obviously it is tempting to suspect from this coincidence in time that a carcinogen may act by interference at some stage in nucleic acid synthesis. Although the question is of course by no means decided, there is much other collateral evidence pointing to a similar conclusion, and Butler in particular has summarised the various effects and actions of x radiation on the one hand, and the alkylating agents on the other, upon the nucleotide chain and its process of duplication (100) A great impetus in this field has been provided both by the new structure of deoxyribonucleic acid, suggested by Watson & Crick, and by its genetic implications; it is not at all beyond the bounds of possibility that carcinogenesis may in fact be an interference with the complementarity of synthesis, based upon deoxyribonucleic acid, which is an essential feature of the new configuration now proposed (101).

Almost as old as the experimental study of cancer is the question whether the process of carcinogenesis should not be regarded as a special case of biological mutation Strong has raised the question whether every mutagen is a carcinogen, and every carcinogen a mutagen (102). While the matter cannot as yet be decided unequivocally, Bird has examined a number of alkylating agents with results which show that the association between carcinogenicity and mutagenicity may be closer here than in any other class, as might perhaps be expected from their marked radiomimetic quality (103). The Fahmys have carried out a cytogenetic analysis of the action of various alkylating carcinogens in Drosophila, with special reference to 1,2, 3,4-diepoxybutane and triethylenemelamine The former substance is characterized by high potency in the production of small deficiencies, with only a small proportion of gross structural change Of special interest are cases in which the bands at the deficiency locus show various "degrees of absence," varying from defects in staining properties to a complete elimination of the band The Fahmys suggest that these "partial expression" deficiencies are the outcome of a modification in the molecular pattern of the gene which has prevented normal reproduction, the disabled gene reproducing itself partially, erroneously, or not at all The general conclusion is an important one, namely, that while x radiation induces chromosome breaks and gross structural change, the radiomimetic mutagens and carcinogens tend rather to produce fewer breaks, and to interfere mainly with the synthesis and reproduction of genetic material (104, 105, 106)

For some time the general biological evidence has suggested that the cancer cell represents a somatic mutation by loss, and the newer advances would seem to enhance this probability, although not as yet conclusively, and to suggest that the deficiency is genetic or enzymic in nature. In particular, it is entirely feasible that the loss of enzyme systems, normally concerned in regulating the synthesis of substances essential to cell division,

zanthracene, an effect which would appear to be peculiar to this particular carcinogenic hydrocarbon (150)

Advances have also to be recorded in the experimental study of tumours of the thyroid, the subject of reviews by van Dyke and by Morris (151, 152). Reference is made especially to the induction of thyroid cancer in rats by radioactive iodine (153), and to the role of thiouracil and propylthiouracil, in the induction, growth, and transplantability of thyroid tumours of the mouse (154, 155). Goitrogen-induced adenomatous neoplasia has also been observed in rat thymus (156). So far as the function of the thyroid itself is concerned, it is of much interest that the hepatoma-inducing action of 2-amino- and 2-acetylaminofluorene is inhibited by thyroidectomy (157).

Numerous papers refer to the induction of hormone- and thyrotrophin-secreting transplantable tumours of the pituitary by "radiothyroidectomy" with iodine-131, their morphogenesis, effects after transplantation on the pituitary body of the host, their initial dependence on the absence of the thyroid gland, and later autonomy (158 to 162). There has also been described the production of pituitary tumours in mice by chronic administration of a thiouracil derivative, and the role of chronic iodine deficiency as a cause of neoplasia in the thyroid and pituitary of aged rats (163, 164). Neoplasms of the pituitary gland in rats, and other tumours, have also followed treatment with pituitary growth hormone (165) An important function of the anterior hypophysis in influencing tissue response to carcinogens is indicated by the inhibition of azo-dye carcinogenesis in hypophysectomised rats, and its reversal by ACTH in synergy with other hormones (166 to 169). Although hypophysectomy has also been claimed to inhibit methylcholanthrene carcinogenesis, the effect is not perhaps so marked or reproducible, and the pituitary would not appear in fact to be essential for the induction of tumours with benzpyrene (170, 171, 172).

Other Carcinogens.—Among types of carcinogenic effect other than those already discussed, one of the most striking is the induction of sarcomas in rodents by embedding various plastic films and fibres, as discovered by Oppenheimer and his co-workers (173, 174, 175). The latest results include positive responses with cellulose in the form of viscose rayon, and with nylon, terylene, and tephlon (personal communication from Dr. B. S. Oppenheimer) A fibrosarcoma has also been induced by embedding silk film—the first instance in which a tumour has been caused by a natural polymer. This phenomenon is not only of the greatest interest in itself but presents special problems as to whether the mechanism of action involves chemical means or, in view of the inert character of many of these substances, a *more physical type of interference* *It also has an obvious practical* bearing in view of the widespread use of synthetic plastics in surgical prosthesis

The unique effects of urethane (ethyl carbamate) continue to be studied with special reference to the induction of pulmonary adenomata in mice

osteogenic sarcoma following x rays (119, 120). It is obvious that the biological hazards of nuclear energy will present problems of increasing magnitude in the fields of industrial medicine and public health administration (121 to 124). The public health aspects of atomic power development have recently been discussed by Warren (125), and in Great Britain the Ministry of Labour has issued a preliminary statement of precautions in the use of ionizing radiations in industry (126). The general problem of leukemogenesis by ionizing radiations has been studied by Furth & Upton (127) This includes data based upon experimental animal material at the Nevada atomic explosions The special problem of the increased incidence of leukaemia in the human survivors of the Hiroshima and Nagasaki explosions is dealt with by Black-Schaffer and others (128). All these matters give added value and importance to the growing number of papers on the radium and radioisotope deposition and retention in the human skeleton and other tissues (129 to 134).

Carcinogenesis and Endocrinology.—Numerous papers continue to testify to the vital role of the endocrine system both in the inception of tumours and in their subsequent growth. Only a few can be mentioned, and discussion on the specially valuable contributions of Huggins, with their applications in practice, is reserved for the section on therapy below. *Oestrogens and Neoplasia* is the subject of a book by Horning & Burrows (135), both of whom have made many contributions to its study In this particular field perhaps the most notable recent work is that of Kirkman & Bacon on oestrogen-induced renal cancer in the male golden hamster (136, 137), a topic which has also been extended by Horning & Whittick with special reference to the histogenesis of these remarkable tumours (138); clearly it will be of the utmost interest and importance if the reason for the species-specificity of the phenomenon can be deciphered Bacon has also described tumours of the epididymis in hamsters treated with diethylstilboestrol and testosterone propionate (139), and more recently Kirkman and his colleagues have also produced specifically localized fibroma-like tumours in this same species by the simultaneous administration of oestrogen and androgen (140). In the clinical field, circumstantial evidence is accumulating to suggest more strongly than before that oestrogen therapy can on occasion be carcinogenic in man (141, 142)

Some of the most ingenious contributions of the last few years on the endocrinology of tumour induction have come from Muhlbock's laboratory in Amsterdam, as for example his induction of mammary cancer in agent-free mice by repeated pituitary implants (143, 144, 145), and his experiments on the origin of ovarian tumours by parabiosis in castrated males (146, 147, 148). It will be recalled that Bielschowsky & Hall described tumours of the ovary produced by 2-acetylaminofluorene in intact female rats joined in parabiosis to gonadectomized litter-mates (149) In another connection, ovarian tumours have also been induced in mice by 9,10-dimethyl-1,2-ben-

cases of cancer (see also 204) as well as their statistical presentation, while third-year recovery and survival rates are recorded by the General Register Office (205). Buckatzsch & Doll (206) have described an experimental factor analysis of cancer mortality in England and Wales from 1921 to 1930, and Stocks (207) the cancer death rates at different ages in England and Wales from 1921 to 1950 in respect to the uterus, breast, and lung Other accounts of special interest are Harnett's *Survey of Cancer in London* (208) and McKinlay's report (209) of the mortality from cancer in Scotland and geographical variations in site incidence. In France, Denoix and his school have studied both global and national cancer morbidity and mortality (210, 211). Similar data are provided from Denmark by Clemmesen & Nielsen (212), while other papers (213, 214), discuss mortality trends. In connection with the earlier work of Berman on primary carcinoma of the liver among the Bantu mineworkers of the Witwatersrand, it is of much interest, and not widely known, that there appears to be a high incidence of the same disease among the population of Haiti, although no published data are as yet available The Negro Republic of Haiti has a dark population of about three millions, composed mainly of descendants of imported African Negro slaves These are known to be the most conservative Negro communities, having preserved their ancient African customs and beliefs Similarly, the major part of the population of Jamaica is of African extraction Recent publications from Jamaica [Hill *et al* (215)] have described hepatic enlargement with fibrosis and ascites in young children, which the authors suspect to be of toxic origin, superimposed on the prevalent malnutrition, and possibly due to "bush tea"—an infusion of various unspecified plants The symptoms described in the Jamaican children closely resemble the early changes seen in rats treated with *Senecio* alkaloids obtained from South Africa (in an extension of Schoental's work referred to above) It seems possible that *Senecio* plants may be used in "bush tea" and that they may be a causative factor in the "serous hepatosis" of the Jamaican children, as well as in primary liver cancer in the adult population in Haiti

Etiology of Cancer of the Lung

The continuing almost world-wide increase in the incidence of cancer of the lung still presents one of the most urgent practical problems in the whole of medicine, and has been the subject of special conferences at Chocorua and Louvain (216, 217) Numerous papers deal with its causation from the aspects of geography, occupation, pathology, and the smoking habit (218 to 228), perhaps the most comprehensive account being provided by Doll's excellent Milroy Lectures to the Royal College of Physicians of London (229) In the first year or two following the independent demonstrations in the United States and Britain of a statistical association between tobacco smoking and lung cancer incidence, there was evident a marked reluctance (partly on the grounds of proper scientific caution but also for human and emotional reasons) to accept the most probable explanation, namely, that

(176 to 182), and a newly recognized effect is the action of this substance as an initiator of skin tumour formation in the mouse (183). For some time the action of urethane has been suspected to concern the synthesis of purines, pyrimidines, and nucleic acids. Indeed Rogers has studied the effect of substances, known to influence nucleic acid synthesis, upon the induction by urethane of pulmonary tumours (184). The inhibition of nucleic acid synthesis, especially with reference to the anti-leukaemic action of urethane, has also been investigated by tracer methods (185, 186). In high concentrations, urethane is a general enzyme poison, but McKinney (187) showed it to be a specific inhibitor of transmethylation reactions when present in low concentrations. For this reason it might also inhibit the transmethylation process involved in the synthesis of thymine and so cause a local deficiency of this particular pyrimidine.

Other instances of specific types of carcinogenesis include the production of hepatic tumours by tannic acid (188, 189), and by prolonged feeding of ethionine (190) or of the alkaloids of *Senecio* (191). Further evidence has also been obtained of the carcinogenicity of the sulphonamides (192). These cases illustrate the wide range of chemical agents capable of inducing a carcinogenic response. It is one of our main tasks to decide whether the ultimate mechanism is fundamentally the same in all these cases, in spite of the variety of initial causes by which the end-result can be evoked.

Apart from purely academic studies, the primary significance of carcinogenic hazards in industry is reflected in reports of occupational skin cancer (193, 194) with special reference to the newer synthetic liquid fuels and petroleum substitutes (195), and of the detection and isolation of polynuclear hydrocarbons from petroleum, industrial effluents, and sewage (196, 197). Among inorganic hazards of special interest are cancer of the lung in the chromate producing industry, and occupational cancer in nickel refiners (198, 199, 200).

Statistics and Demography

Recent years have witnessed a most fruitful application of statistical techniques to cancer research, in many cases along the lines inspired and still continued by Kennaway. Of this process the most dramatic outcome, namely, the elucidation of the role of smoking in the causation of cancer of the lung from numerous American and British reports which are mutually confirmatory to an astonishing degree, will be discussed in more detail below. In addition, however, there are many recent compilations of great value, as for example the section on cancer of the Epidemiological and Vital Statistics Report of the World Health Organization (201), a symposium on Geographical Pathology and the Demography of Cancer under the auspices of the Council for the International Organization of Medical Sciences (202), and the Proceedings of the International Conference on Geographical Pathology held at Washington in 1954. In England, the Report of an Expert Committee on Health Statistics (203) includes information on the registration of

the development of mammary tumours has been known for some considerable time, and is further illustrated by studies of the occurrence of such tumours in agent-free pure lines (243, 244). In Mühlbock's view, the agent may accelerate the appearance or increase the number of hyperplastic nodules in the mammary tree without directly affecting their conversion to malignancy.

The rabbit papillomas and papilloma viruses have been reviewed by Ginder (245), and the induction of the Shope papilloma in homologous transplants of embryonic rat skin reported by Greene (246) The electron microscopy of rabbit papilloma has been investigated by Kahler and his colleagues, with reference to the occurrence of crystalline plates (247, 248), and Bunting describes a close-packed array of virus-like particles within the cells of a human skin papilloma (249). Other interesting observations are of cutaneous sarcoma-like lesions of the mouse caused by the agent of bovine papilloma, and the laboratory transmission of the Shope fibroma in cottontail rabbits by means of fleas and mosquitoes (250, 251). Smith and others have discussed the cause of the rabbit carcinomas derived from virus-induced papillomas (252) In the writer's own view the relationship is not a primary one, and this agent again may be of the kind responsible for antecedent changes, although not for malignant transformation itself.

Following upon his earlier studies of the so-called "vertical" transmission of mouse mammary cancer and chicken leukaemia, Gross has made a remarkable discovery which, if fully confirmed, must have profound implications not only for animal pathology but possibly for human pathology as well; namely, of a virus-like agent in mouse leukaemic and embryo tissue of the AK line (and in the testes and ovaries) capable of transmitting the disease by way of extracts or filtrates to C_3H mice less than 10 hr. old (253, 254, 255). The same procedure also induces salivary gland carcinomas (256, 257). Some confirmation of the latter observation appears to have been obtained by Law (258) and by Stewart (259), but clearly the phenomenon requires extended investigation before its reproducibility can be fully assessed or its interpretation defined. Again, it may well be that the agent is one affecting susceptibility to the leukaemic transformation Also, the writer has been impressed with the possible relation of these results to the recent discovery by Billingham and Medawar of the induction of acquired tolerance in the adult by pre-treatment of the embryo with relatively foreign cells

Studies continue to be made of the avian leukaemia viruses by electron microscopy and physico-chemical methods, especially of the particles isolated from the plasma of affected fowls (260 to 263) Some advance has also been reported in the electron microscopy of the Rous sarcoma and agent, and interesting micrographs have been obtained by Bernhard *et al.* (264), and Bernhard & Oberling (265), and by Wyckoff (personal communication) The whole problem of viruses in relation to cancer continues to present many paradoxes and difficulties Yet all the facts must obviously be accounted for in an eventual solution, and, in the writer's view, there is no necessary antithesis between the facts and those interpretations of chemical carcinogenesis

the association is causal A valuable and more recent compilation of scientific and professional opinion is given in a special number of the *Medical World* (230), but even since that date it is obvious that opinion has hardened very considerably; there is no longer any serious remaining doubt, even when all possible allowance has been made for such factors as improved diagnosis and alterations in the age structure of the population, that part of the recorded increased incidence is undoubtedly real, and that the cigarette habit is responsible for a considerable fraction thereof. This consolidation of opinion is based not so much upon the demonstration of carcinogenic properties in cigarette smoke and tar (231, 232)—which must still remain somewhat inconclusive so far as lung cancer in man is concerned—as upon the overwhelming weight of Doll & Hill's "forward survey" of the mortality of doctors (233) and apparently of Hammond's similar survey in the United States, of which only press reports are available at the moment of writing

Even although it may be regarded as proved that the smoking habit is a potent determinant of cancer of the lung, the mode of action is by no means clear; many find it difficult to believe that increasing atmospheric pollution plays no part, especially in view of the increased incidence of the disease in urban as compared with rural areas (234). This difference may, however, be showing some tendency to decrease. In addition to the earlier contributions of Kennaway, atmospheric contamination and carcinogenesis has recently been considered by Clemo (235) and by Kotin *et al.* (236, 237), the last in relation to aromatic hydrocarbons and other carcinogens in the Los Angeles atmosphere and in gasoline-engine exhausts

The whole subject is now under intensive investigation, notably with the guidance of the Medical Research Council in Great Britain, and of the Tobacco Industry Research Committee in the United States Elucidation may not, however, prove easy, and the need for research must not obscure the fact that abolition of the cigarette (which the latest data incriminate more seriously than the pipe or cigar, if not exclusively), would effect the greatest step in cancer prevention available to us today.

Tumour Causation and Viruses

While so much attention has been given to chemical carcinogens, the continued presence of which is no longer required when once they have provoked the malignant transformation, no less important are the so-called tumour viruses, which in many cases appear to have an essential function not only in the instigation of tumours but also in their subsequent growth. Vigorous accounts of the more recent development of the virus hypothesis of cancer causation have been given by Oberling (238) and by Oberling & Guérin (239), and the field has been surveyed in detail in a symposium under the auspices of the New York Academy of Sciences (240)

So far as concerns the agent for mammary cancer in mice, perhaps the most interesting papers are those on its possible transference by the male (241, 242). The apparent lack of any strictly essential role of the agent in

biotic inhibitor of amino acid synthesis, which it should be noted can be regarded as an alkylating agent of un-ionized groups such as sulfhydryl. While many studies have been made of its microbiology and mode of action, the clinical application of azaserine requires further assessment and is not perhaps too promising (286 to 291). Others are the antimetabolic dihydrotriazines investigated by Farber *et al* (292, 293, 294) and Foley (295); methyl-colchicine (Demecolcin-Ciba) in the treatment of chronic myelogenous leukaemia [Moeschlin *et al* (296, 297)]; the radiation-protective agent β-mercaptoethylamine in the chronic leukaemias [Bacq and others (298, 299, 300)], phenylbutazone (Butazolidine) (301); and various ali-esterase inhibitors (302).

Endocrine Therapy—The treatment of prostatic cancer by orchiectomy and with oestrogens was perhaps the first substantial contribution to cancer therapy other than by orthodox methods. In the hands of Huggins and his school the whole question of the endocrine control of human cancer, by steroid modification of the internal environment, has continued to develop, especially with reference to the inhibition of mammary and prostatic cancer by adrenalectomy (303 to 310) Although no final conclusions can as yet be reached, the principles which govern this procedure, and the conditions under which it may be expected to give benefit, both continue to clarify; it would seem that the response of breast cancer to adrenalectomy is probably greater in adenocarcinomata than in more undifferentiated types, in cases which show longer intervals in the developing of metastases, and in those with an increased oestrogen excretion (311, 312) Many independent papers continue to appear upon the clinical results and their structural basis (313 to 317). Of closely related interest are descriptions of the influence upon prostatic cancer, and other tumours, of pituitary x-irradiation or hypophysectomy (318 to 321); while of occasional undoubted usefulness in palliation, it seems doubtful whether either procedure can have any more than a strictly limited application The hormonal treatment of cancer of the breast continues to be evaluated, with reference also to the action of methylandrostenediol, and to the effect of cortisone treatment on the urinary oestrogens in postmenopausal women (322 to 329). Although of the highest potential importance, the fundamental mechanism of action of oestrogens upon breast cancer still eludes us

A Panel on the Haematological Applications of ACTH and Cortisone has presented a second report to the British Medical Research Council (330) and further accounts have appeared of the influence of cortisone and ACTH in the reticuloses and acute leukaemias of both children and adults (331 to 334) In the case of the acute leukaemias in patients over the age of 20, fairly general experience seems to indicate the use of cortisone, not of the antifolics.

Two papers of exceptional interest report the influence of thyroid hormone on the growth of experimental thyrotrophin-secreting pituitary

in terms of enzyme modification or loss, which have been briefly dealt with above.

Chemical and Endocrine Treatment

General.—If the bulk of cancer therapy is still surgical or radiotherapeutic, the limitation of these orthodox methods continues to be ever more clearly defined. There has recently developed, particularly in England, a much more critical attitude than heretofore on such questions previously commonly accepted, as the value of early diagnosis in relation to treatment. In many cases the argument is extreme or even heretical, but it cannot nevertheless altogether be ignored (266, 267, 268). So far as radiotherapy especially is concerned, its immediate past and future have been appraised by Wood (269) while Mayneord (270) and Brucer (271) have provided valuable surveys of the clinical application of radioactive isotopes. There appear to be some 70 radioisotopes with half-lives between 12 hr. and 60 days which might be produced in sufficient amount to be useful from the therapeutic standpoint. In practice, the number is nearer 25 or 30, while contamination with long-lived activities, and competing reactions, tend to reduce the list still further While there would appear to be no question of the value of such agents as radiophosphorus in the treatment of polycythaemia, chronic myeloid leukaemia, and multiple myeloma, of radioiodine in thyroid carcinoma, and of radiosodium and radiogold in other applications, much further critical research is required So far the most significant applications of the radioisotopes have been in the field of biochemistry rather than of therapy. The very limitations of surgery and radiotherapy are the main stimulus to research, in the hope of developing a rational chemotherapy based upon complete understanding of the carcinogenic process This stage is still far from attainment, but chemical agents which are of unquestioned clinical usefulness have meantime become available, even although their application is severely limited and must be subject, no less than for radiotherapy and surgery, to the most critical assessment This is specially so for single cases, in view of the exceptionally long individual survivals which are not infrequently recorded in the chronic leukaemias, in breast cancer, and even in such conditions as malignant melanoma (272 to 275).

Good general accounts of the basis and practice of chemotherapy in cancer have recently been given by Burchenal (276), Truhaut (277), Pirwitz (278), Stock (279), Rhoads (280), and Boyland (281), its special application in the treatment of the malignant lymphomas and leukaemias has been assessed by Rundles (282), Dubois-Ferrière (283), Moeschlin (284), and Lien-Keng (285).

The agents in current use may be divided roughly into two classes: those which have been too recently described to permit a final assessment, and those whose usefulness and limitations are already moderately clear The former include azaserine (0-diazoacetyl-L-serine), a remarkable anti-

tent treatment, and of the role of the antifolics versus ACTH therapy, is given in the proceedings of the Second Conference on folic acid antagonists (360), while more recent papers deal with newer derivatives such as dichloroaminopterin (361). As to mechanism of action, Sauberlich has described the reversal of aminopterin toxicity in the rat with citrovorum factor, pteroylglutamic acid (folacin), and related compounds (362), and Boyd & Delahaye the neutralization of aminopterin-induced leucopenia with adenosine-5-phosphoric acid (363) The antagonists 2,6-diaminopurine and 8-azaguanine operate by somewhat similar mechanisms, both being incorporated with nucleic acids in the mouse (364, 365), in neither case however is their therapeutic action as marked, although according to Dietrich & Shapiro it can be potentiated by a riboflavin analogue (366). In the last connexion, it may be noted that acquired chemoresistance, which is a limiting factor in so many examples of cancer chemotherapy at the moment, is believed by some to be slower to develop in response to combinations of inhibitors than to the same inhibitors singly; this opinion is not, however, by any means universal The past two years have seen a vigorous investigation of one of the more recent additions to the list of metabolic antagonists, namely, 6-mercaptopurine, including studies of its effects upon animal tumours (367), its mechanism of action as revealed by microbiological studies (368, 369, 370), its distribution and incorporation with the tissues (371), and its clinical effects, especially upon the leukaemias in man (372) Although clinical responses tend to be somewhat erratic and unpredictable in their incidence, a proportion are dramatic in nature and can equal the best to be obtained with any other agent or form of therapy A full assessment is to be found in a recent symposium of the New York Academy of Sciences (373).

Lastly may be noted an observation made at the Hospital for Sick Children, Great Ormond Street, London, England, which if confirmed, will be of much importance, namely, that administration of vitamin B_{12} results in tumour regression in a fair proportion of cases of neuroblastoma—enormously more than could be accounted for by the recorded tendency of such tumours occasionally to undergo regression spontaneously (374) The influence of vitamin B_{12} upon experimental animal tumours had already been studied by the writer with essentially negative results, and its failure to affect acute leukaemia has already been reported (375).

Oncolytic Action of Viruses—Following the earlier reports by Moore and her colleagues, and others, of the inhibitory effects upon tissue cultures and transplantable tumours of the Egypt virus 101, and the virus of Russian Far East encephalitis (376 to 379), clinical studies (380) do not appear to have offered any very substantial prospect of general application On the other hand, the subject still remains of potential practical value—in additon to being of intense theoretical interest—as is shown by accounts of the effect of Semliki Forest virus on rabbit myxoma (381), the propagation of St. Louis encephalitis virus in cells of the Ehrlich ascitic tumour (382), the

tumours (335) and the successful treatment with thyroxine of metastatic carcinoma of the thyroid (336).

Cytostatic Agents—Papers upon the clinical application of triethylenemelamine (TEM; above), and of other polyethyleneimines and related cytostatic agents such as the triethylenephosphoramides, continue to appear in such numbers as preclude their individual mention (337 to 347). In general, TEM is capable of inducing dramatic objective responses in selected cases of lymphosarcoma, Hodgkin's disease, and chronic myeloid and lymphatic leukaemia—the last being exceptionally sensitive so that the very closest clinical and haematological supervision is required. Responses in lymphosarcoma, reticulum-cell sarcoma, and mycosis fungoides are on the whole less marked. In comparison with nitrogen mustard, TEM possesses the advantage of oral administration and moreover induces fewer side-reactions, but it has the disadvantages of a narrower chemotherapeutic range and may produce bone-marrow depression which occurs later than with the mustards, lasts longer, and may be irreversible. In spite of the limitations of all substances of this general class so far examined, there is no question of the value of further search. Individual recent examples include a bis (ethyleneiminosulphonyl) propane (348), and an imine based upon benzoquinone [Domagk *et al* (349)], while the writer's colleagues have prepared a series of carboxylic derivatives of NN-di-2-chloroethylaniline (350) and various mustard derivatives of amino acids and peptides (351), certain of which are of high activity and are under clinical trial Even so the limitations of this approach are evident, and it may well be, as already suggested, that the real value of such chemical agents lies in their fundamental interest, the pursuit of which may lead to fresh advances which will render obsolete their present-day chemotherapeutic application Although it appears doubtful, for instance, whether the use of such cytotoxic agents has in fact led to any material change in prognosis, there may, however, be exceptions, as in the case of the treatment of myelomatosis with a combination of urethane and an aromatic mustard (352), or of the application of myleran (1,4-dimethanesulfonyloxybutane) in chronic myelogenous leukaemia (353, 354, above). In a proportion of selected cases, even when radio-resistant, the last compound has yielded results which, in substantial clinical usefulness, are perhaps the equal of any chemotherapeutic agent encountered thus far Although several independent studies are beginning to appear, the basis of its relatively selective action against the myeloid series is still unknown (355 to 358).

Metabolic Antagonists—After several years of careful clinical trial at a large number of centres, it would seem that the most favourable results so far observed in the treatment of acute lymphatic leukaemia and stem cell leukaemia in childhood have been obtained with aminopterin and related compounds, numerous cases having been reported of remissions lasting over one year, during which time many appear practically normal (359) A useful discussion of the advantages and disadvantages of continued and intermit-

on intracranial tumours (416, 417), congenital sarcoma (418), chronic myelogenous leukaemia (419, 420), Hodgkin's disease (421), cardiac tumours (422), phaeochromocytoma (423), extra-adrenal tumours of the sympathetic nervous system (424), and tumours of the ovary (425), testis (426), epididymis (427), thyroid (428) and liver (429, 430). The radiotherapy of tumours in children has been discussed by Phillips & Dargeon (431). From the above, and for several reasons, it would appear highly desirable to establish the true incidence of cancer in childhood, and to decide whether these papers are published because of the essential rarity of the conditions they describe, or whether they reflect a real increase

Referring especially to leukaemia, attention must be drawn to an excellent account of the dynamics of haemopoiesis by Whitby (432), to Bessis's *Traité de cytologie sanguine* (433), and to the survey by Gauld *et al.* of over 600 cases between 1938 and 1951 (434). Multiple myeloma and the reticuloses have been the subject of clinico-pathological studies by Snapper *et al.* (435) and by Israels (436).

Of recent years, several papers have referred to a condition which, if authenticated, would unquestionably possess a wider theoretical significance, namely, multiple primary, spontaneously healing, squamous cell carcinomata of the skin (437, 438) It is therefore of importance that the relationship to this condition of that known as molluscum contagiosum, or kerato-acanthoma, has been made the subject of careful study by Fouracres & Whittick (439, 440), leading to the conclusion that the so-called self-healing epitheliomata are probably only molluscum and must therefore be denied the significance which they otherwise might have had

Other contributions of exceptional merit are an excellent account of malignant cachexia by Donovan (441), and a continuation of Handley & Thackray's study of the invasion of the internal mammary lymph nodes in cancer of the breast (442).

ENVOI

What is the present position in cancer research? After 25 years of experience, the writer's main impression is one of ceaseless change, and the period under review is no exception While much of this change is of emphasis, the intricacies of the subject must not be allowed to obscure the emergence of real trends Although almost infinitely complex in their detailed manifestations, it is probable that the underlying biological principles are of startling simplicity In a recent lecture to the Royal Institution in London, Sir Lawrence Bragg related how, after the discovery and application of x-ray analysis, much of mineralogy could be written on the back of a postcard, the new technique having revealed Nature's unique methods for the construction of an infinity of minerals Although the present case is not perhaps a parallel, the latest suggestions as to nucleic acid structure do in fact suggest that Nature may here also employ a unique code, with which to spell out an infinity of diverse proteins, and that malignant change may indeed spring

inhibition of the growth of the Ehrlich carcinoma by the virus of Newcastle disease (383), and the destruction of tumour cells by the virus of Rift Valley fever (384).

Clinical and Clinico-Pathological Papers

From a great flood of papers in the clinical or clinico-pathological fields, only a relatively few can be selected to illustrate items of special interest Thus contributions have been made to what may be called the concomitant pathology of cancer, particularly intriguing examples being the associations between thrombophlebitis migrans and carcinoma of the body and tail of the pancreas (385, 386), between carcinoma and proximal motor neuropathy (387, 388, 389), and between bronchial neoplasm and myasthenia (390, 391). The description by Aird and his co-workers (392) of a relationship between cancer of the stomach and the ABO blood groups has stimulated much further work (393, 394, 395) While the importance of the subject is obvious, especially from the aspect of cancer causation, a greater body of data is required before its general or special significance can be fully assessed, and the meaning of these correlations explained

In the field of diagnosis, important contributions have been made in Papanicolaou's *Atlas of Exfoliative Cytology* (396) and a *Bibliography of the Cytologic Diagnosis of Cancer* issued by the U S Public Health Service (397) A further useful application of these methods, in the control of occupational cancer of the bladder, is recorded by Crabbe (398) Cancer diagnostic tests generally have been surveyed in a publication of the National Cancer Institute (399), and Girdwood (400) has carried out studies on folic acid excretion in relation to malignant disease, which might conceivably allow a limited diagnostic application

The familial aspect of cancer in man has been illustrated by accounts of multiple osteomas in a family group (401), of acute leukaemia in twins (402, 403), and of heredity in uterine cancer (404), while Dukes has extended his well-known studies of familial intestinal polyposis in a Hunterian Lecture to the Royal College of Surgeons of England (405, 406) Dukes and others have also investigated the relationship to carcinoma of the rectum and colon of chronic ulcerative colitis (407, 408)

A particularly significant group of papers recounts instances of remission in acute leukaemia in children, either spontaneously or following acute infectious disease (409, 410), and of spontaneous regression in Hodgkin's disease and prostatic carcinoma (411, 412) The whole question of the spontaneous regression of neoplastic diseases in man has been surveyed in an important contribution by Stewart (413)

A special feature of the period under review has been the unusually large number of papers dealing with malignant disease in childhood Again, only a fraction can be noted, but mention may be made of Fèvre & Huguenin's book on *Malformations tumorales et tumeurs de l'enfant* (414), of Bufkin & Davison on childhood cancer (415), and of individual contributions

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from a derangement of this essentially genetic process. Short of happy accident, the best prospects for the solution of the cancer problem would appear to lie in fundamental biology. Whether it is most likely to be accomplished by erstwhile methods, and how far the process is likely to be expedited by an international extension of research such as is shortly to be considered by UNESCO in collaboration with the World Health Organization, are matters for future policy. But any who doubt the main thesis are well advised to read Bashford's prophetic account, written in the early years of the century and reproduced in the third Scientific Report of the Imperial Cancer Research Fund of which he was the first director, and to judge how much of what he then forecast has meantime been accomplished, and how much remains to be done.

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DISEASES OF THE NERVOUS SYSTEM[1]

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Introduction

In writing an *aperçu* of neurological studies made over the last few years, one is faced with a difficult decision. The world's literature has contained in the last quinquennium works of two contrasting classes First there is a larger group, made up of worthy contributions of a descriptive sort. These comprise reports of clinical observations; new techniques and findings in neurosurgery; experiences with drug therapy; neurophysiological spadework (with special reference to electrical methods); and lastly, the traditional strategy of neurology, namely, clinico-pathological correlation. There has been work of this sort in abundance, emitting from neurological clinics throughout the world Perhaps the volume of output is on the whole disappointing Possibly the nature of the work done falls short of the ideal, being more a testimony to personal industry than to intellectual brilliance. As a contrast to this solid bulk of descriptive, representational material, there is the other class of neurological contribution. This is much smaller in quantity. It comprises those studies where known data, some of them perhaps so familiar as to be commonplace, are taken, re-examined, and reorientated. Novel ways of critical thinking are adopted, rather than new techniques. The result is an exercise in creative thought as well as in critical appraisal, and speculative thinking rather than painstaking description becomes the aim. To embark upon such a work is to run great hazards A descriptive piece stands or falls by the detail and accuracy of the observations The dangers, as well as the rewards, of speculative thought and intellectual judgment are much greater, and he who treads the path of creative thinking must walk warily.

Certain neurological centres are attracting attention by reason of the high quality of their researches today It would be invidious perhaps to specify but it is difficult to avoid mentioning the steady stream of excellent work which is emerging from renascent Germany This particular type of neurological work is extremely difficult to evaluate and condense within such a medium as the *Annual Review of Medicine*, except as a bare catalogue of excerpts. It is therefore deemed more worthwhile to concentrate upon the former class of clinico-pathological studies, which might be called the fact-finding of traditional neurology

Tumours of the Glomus Jugulare

Although "aberrant carotid body tumours" have been recognised for years, otologists rather than neurologists have regarded them as lying within

[1] The survey of literature pertaining to this review was completed in June, 1954.

their own province. Quite recently, and quite suddenly, the situation has changed, and neurosurgeons now realise that a new entity in the subject of tumours of the glomus jugulare lies within their legitimate sphere The first case of this kind was reported in New York by Rosenwasser (1), though in retrospect it seems possible that the case recorded by Lubbers of Amsterdam (2) was of this type Much of our present day awareness is attributable to the work of Hooper of Melbourne, who has drawn attention to a syndrome which is reminiscent of a cerebellopontine angle tumour. A condition of middle ear deafness goes on to nerve-deafness, and later includes a loss of vestibular function With some abruptness a peripheral facial palsy then develops on the same side as the deaf ear, followed a little later by some objective sensory loss within the homolateral trigeminal territory Then comes a pulsatile tinnitus which may be audible to others as a cranial bruit. Little or no headache occurs Skiagrams of the skull may reveal an excavation of the petrous bone

Within the last 12 months papers have appeared in Israel by Askenasy, Eppenstein & Herzberger (3), in London at the hands of Henson, Crawford & Cavanagh (4), in Birmingham by Bickerstaff & Howell (5), and in Brussels by Carbone, Martin & Branden (6). The two British communications, which were issued independently and yet almost simultaneously, form an interesting contrast of two methods of approach to the same clinical topic.

The work of Lecompte (7) and of Guild (8, 9) has drawn attention to the anatomy of the subject A chemoreceptor system of structures lies in association with the thorax, heart, and head and is made up of the carotid body (the largest of them), the aortic group of bodies, the glomus tympanicum, the auricular bodies, and one or more little structures lying in the dome of the jugular bulb The last-named comprise the glomus jugulare It is to be found near the ramus tympanicus and the glossopharyngeal nerve As a rule there is but one of these structures, a flattened ovoid body measuring about 0 5 mm by 0 25 mm Occasionally two or more smaller bodies are present Sometimes one or all are in the canal transmitting the ramus tympanicus through the floor of the middle ear Each glomus consists of blood vessels of capillary or pre-capillary calibre with numerous epithelioid cells between the vessels These are arranged in whorls or clusters (*Zellballen*) They are invested by collagenous tissue Histologically the structure resembles that of the carotid body

According to Magarey (10), the first to describe the glomus jugulare was Valentin (11) in 1840, under the term *gangliolum tympanicum*, and it was rediscovered a century later by Guild (8) (whose latinity was at fault when he spoke of a glomus "jugularis," later corrected to "jugulare")

The histological term applied to these tumours has varied Some have spoken of *non-chromaffin paragangliomas*, others of *haemangeio-endotheliomata;* or *granular-cell myoblastomata* Carbone *et al* (6) specify that there are three types of glomic tumours (*a*) those reproducing the normal structure of the glomus, (*b*) an adenomatous type with a preponderance of epithelioid cells; and (*c*) an angeiomatous type, especially rich in capillaries.

Most of the case records of the clinical effects of tumours of this structure in the literature have been published by otological surgeons, but pathologists and neurosurgeons have also contributed [Rosenwasser (1); Kipkie (12), Lecompte, Sommers & Lathrop (13); Lattes & Waltner (14); Lundgren (15); Berg (16); Poppen & Riemenschneider (17); Terracol & Guerrier (18); Winship & Louzan (19); Black (20); Capps (21)]. Approximately 100 cases are now on record. The ages of the patients have varied widely, the extremes being 17 to 81 years, but the majority of them have been middle-aged. Women seem to have been affected considerably more often than men, the proportion being 4 or 5 to 1. (This preponderance contrasts with the case of tumours of the carotid body where the incidence is approximately equal in the two sexes). The length of the history has been comparatively great, in some cases over 20 years. As regards the clinical picture, Bickerstaff & Howell (5) have isolated four main types: (*a*) those with aural symptoms only; (*b*) where aural symptoms were followed years later by signs of neurological involvement; (*c*) cases in which nervous and aural symptoms developed together, and (*d*) cases where neurological features have antedated aural signs These four groups may be considered separately

Aural symptoms only—This is the commonest experience. The picture is made up of progressive deafness and a rushing or roaring tinnitus Less often a discharge from the ear may occur, possibly offensive Vertigo and earache are both rare Special note is made of bleeding from the ear after coughing, sneezing or straining, or even on washing the ear. Inspection of the ear shows a reddening, bulging, or pulsation in the postero-inferior portion of the drum. [Magarey (10) has graphically described the aural manifestations by saying that in the early stages the colour of the drum head is gun-metal blue, gradually changing to dark plum. Later a small, raised, strawberry-like area appears in the lower posterior segment of the drum, which may remain unchanged for the next 12 to 18 months]. Tympanic puncture is followed by profuse haemorrhage Later still a polyp may grow through the drum and present itself at the external meatus Or the polyp may erode into the meatus and show itself covered by squamous epithelium Any form of surgical intervention leads to much bleeding

A facial palsy, often sudden in onset, is the only neurological complication

Neurological signs following aural symptoms—In these cases an interval of at least 10 years may separate the aural from the nervous manifestations. Extension of the growth in a caudal direction brings about an involvement of the ninth, tenth, eleventh and twelfth cranial nerves (The syndrome of the *foramen lacerum posticum* is particularly suggestive here) The patients first complain of difficulty in swallowing and of hoarseness By this time the facial nerve, too, is probably paralysed Much more rarely are the fifth and sixth cranial nerves implicated In one recorded patient, the tumour extended forwards and caused a unilateral proptosis Signs of increased intracranial pressure are rare Involvement of the pyramidal tract is not common, but ataxia may result from compression of the cerebellum The authors draw attention

to two other characteristic clinical findings. Sometimes the tumour presents itself high in the neck, in front of and just below the tip of the mastoid process, as a pulsatile lump which may transmit a thrill to the lobe of the ear. Secondly, a bruit may at times be audible over this mass; or, if no lump presents itself, over the mastoid, the temporal bone, or the cheek. X-rays of the skull, in such patients, may show erosion of the petrous bone, enlargement of the jugular foramen and even thinning of the occipital bone. Carbone *et al* (6) emphasized that the bony infiltration is not so much an osseous destruction, as a "colonization" or invasion of the bone by the growth, analogous to that occurring in cases of meningioma. It is believed that the epithelioid cells pass by way of the Haversian canals to settle and proliferate within the bone around the blood vessels which in their turn increase in number and in thickness.

Simultaneous development of aural and neurological signs.—Such tumours have probably arisen near the origin of the tympanic nerve. Here the course is a more rapid one, and the brain-stem may become compressed.

Nervous manifestations first.—Such cases form the smallest group.

The neurologist, in all these cases, will be impressed by the association of a haemorrhagic aural polyp with a unilateral paralysis of the lower group of cranial nerves Angiography may assist diagnosis by revealing a diffuse opacity of the region occupied by the tumour.

There are one or two other interesting clinical points which seem, however, to be exceptional There may be a familial incidence. Multiple tumours of the chemoreceptor group may occur [Askenasy *et al.* (3)]. Rarely, visceral metastases may develop [Bronzini (22)] Trauma may apparently precipitate the development of new-growth formation [Terracol & Guerrier (18)]

Radical surgery is not promising in cases of tumours of the glomus jugulare. Aural surgeons may no doubt be able to cope with patients belonging within the first group In the last three groups, however, deep x-ray therapy, perhaps combined with a ligation of the external carotid, may be practised as a palliative measure

Nervous Complications of Scrub Typhus

Noad & Haymaker (23) have studied the neurological features of scrub typhus (*tsutsugamushi fever*) with special reference to the complication of deafness Although scrub typhus constituted at one time a dangerous hazard of warfare in the Far East, it is unlikely to become, in peace-time at any rate, an important source of ill-health In large measure, this favourable change arises from the introduction of chloramphenicol (chloromycetin), which was, of course, not available during the war years. This study has been based upon the medical records of 180 Australian soldiers who had contracted scrub typhus in New Guinea In the early stages of the disease, muscular weakness or sensory symptoms (or both) occurred in 10 out of the 180 patients (5 5 per cent) These symptoms were looked upon as the effects of lesions of the nerve roots or trunks. The clinical manifestations could not be

regarded as very intense, and by 1949 the signs had cleared up in 9 out of the 10 patients. The tenth patient showed symmetrical wasting of the upper trapezii, with winged scapulae, and it was possible that the scrub typhus was not to be inculpated [Wolf seems to have seen two similar cases (24)]. During the acute phases of scrub typhus, convulsive seizures were not rare, particularly in patients who later died. In three patients the fits recurred after the disease had cleared up From the total of 180 cases, 40 patients continued to complain of various psychological symptoms One patient was unusual in that he developed a dementia, an epilepsy, and an extrapyramidal type of motility-disorder. This was the only such case in the Noad-Haymaker series, though Ripley (25) had previously mentioned this sequel also, as occurring once in his 50 patients. Another patient showed a mental disorder which was very reminiscent clinically of general paresis Convulsions had occurred on the twenty-ninth day of the illness, and the patient also developed a grasping phenomenon in the right hand, a dysphasia, and constant sucking movements A third patient after scrub typhus passed into a hypomaniacal state with headaches, giddiness, and irritability. Yet a fourth patient suffered a transitory paranoia About one-third of 106 patients (38 per cent) complained of what the medical officials dubbed a "post-typhus syndrome," i e, a combination of easy fatiguability, lack of energy and initiative, headache, timidity, and breathlessness

Most attention was paid to the affections of hearing during and after an attack of scrub typhus. Ripley noted deafness in 46 out of 50 patients during the acute stages. Dame (26) noted aural symptoms (deafness, tinnitus, earache, vertigo) in half of his 50 patients during the first week and in three-quarters during the second week of the illness Macaskill (27) had also called attention to nerve deafness in scrub typhus Noad & Haymaker examined the brains of 16 fatal cases of scrub typhus and in each instance the auditory nerves were specifically scrutinized Changes within the cochlear nuclei were few and equivocal. By exclusion, therefore, the permanent type of deafness was regarded as being due to irreversible changes in the internal ear or else in that part of the eighth nerve which lies within the internal auditory meatus Transient disorders of hearing noticeable in the acute stages of the disease may be a result of a relative circulatory failure (ischaemia) of the glial part of the acoustic nerve

Noad & Haymaker's article should be studied alongside the earlier and detailed papers of Ripley (25), Reynes & Richard (28), Poinso (29), and Ragiot & Delbove (30)

Ripley's series comprised 50 service patients who contracted the disease on Goodenough Island, near New Guinea Every patient had headache, and all but 5, anorexia; 28 had nausea, 22 vomiting. The most frequent indications of neural involvement were deafness, 34; tinnitus, 26, bodily pains, 25; pain on movement of the eyes, 18; incontinence of urine, 17; muscular twitchings, 17; impaired vision, 17, hiccup, 10; meningismus, 5; and urinary retention, 3. Changes in the reflexes were found, either in the direction of

diminution or exaltation. In a few patients there were also convulsions, dysarthria, difficulty in swallowing, squints, pupillary inequality, inability to protrude the tongue, and alterations in sensibility.

Unusual neurological sequelae occurred in two or three. There was one case of acute Parkinsonism (already mentioned). Another patient recovered from coma to suffer intense dysaesthesiae in the legs with objective sensory loss lasting some weeks Yet another patient developed burning feet and numbness of the thigh.

In almost every patient, mental symptoms were present. These included disorientation, 34; difficulty in concentration, 31; loss of memory, 30; delirium, 29; coma, 17; hallucinations, 17; delusions, 24. One patient had a Korsakoff psychosis During the stage of convalescence, other psychological features developed, e.g, illusions, feelings of unreality, apathy, *déjà vu* states, anxiety, irritability, and depression

Examination of the spinal fluid gave abnormal results in seven out of eight cases, comprising a mild cellular and protein increase.

Autopsies were performed in 13 cases Oedema of the brain was found three times, with flattening of the convolutions; congestion of the blood vessels was also found at times, as well as leptomeningeal haemorrhages One case was studied in greater histological detail, and changes very like those of typhus were found.

Diabetic Neuropathy

The early history of diabetic neuropathy can be traced back as far as Rollo (31) and Marchal (de Calvi) (32). Recently the subject has been studied with care by Hirson, Feinmann & Wade (33) and by Martin (34). The former group of authors found 57 examples of neural anomalies out of a series of 100 diabetic outpatients, a proportion not very different from that observed by Jordan (35), who encountered neurological changes in 45.3 per cent of diabetics, with 2 5 per cent cases with "real neuritis."

Hirson, Feinmann & Wade made a rather unusual classification thus (*a*) hyperglycaemic neuropathies; (*b*) active neuropathies; and (*c*) asymptomatic neuropathies The first of these included acute states of pain and paraesthesiae, with but few abnormal signs, coming on with the onset of hyperglycaemia, and being rapidly relieved by appropriate treatment The second group comprised cases with diverse clinical features, where a tendency to spontaneous relapse and remission was common The third group was made up of cases with objective rather than subjective features, i.e., reduction or absence of tendon jerks, loss of vibratory sensibility, and of deep pressure sensation Pupillary changes were present at times The authors obviously found difficulty in making a logical classification of the neural complications in diabetics, for any level of the nervous system may be affected Among the neural manifestations the authors mention pain in the limbs which is cramp-like, twitching or burning, and worse at night; weakness and wasting of the

quadriceps femoris muscle on one side or both; painless gangrene; arthropathies; retention of the urine, nocturnal diarrhoea; and cranial nerve palsies. It is clear that such a miscellaneous collection of clinical features strains attempts at classification The authors do not believe there is any good evidence that the nervous complications are any fewer now than they were in the pre-insulin days. They suggest that diabetes is a disease-complex in which the metabolic disorder is only one manifestation, with neuropathy occurring not as a "*complication*" *but as an integral part of a variable process* There is no good evidence, they say, that either arteriosclerosis or a vitamin B_1-deficiency is a causal agent.

Martin's series comprised 150 cases, found in patients attending the diabetic clinic of a London general teaching hospital. Peripheral nerve disease occurred at any time in the course of the metabolic disorder. The patients most prone to develop neuropathy were those mild diabetics who were able to carry on in a state of therapeutic neglect, without disabling symptoms or ketosis, for long enough to develop the various complications Seventy per cent of the patients were over the age of 50. Diabetic neuropathy was found to be relatively uncommon in the youngest age groups, though by no means rare. There was a preponderance of male over female patients The author considered carefully the neurological clinical picture. Always, the lower limbs were more affected Early symptoms were often those of aching, cramps, dysaesthesiae, and weakness (especially of the quadriceps) The patients found difficulty in getting up from a chair, in getting off and on buses and trains, and in climbing stairs As a rule, by the time the patient sought medical advice, physical signs were demonstrable. In 40 per cent of the cases, the disability was regarded as being considerable, the pains being intense, and the weakness marked, and accompanied by wasting and objective sensory impairment In some instances, there was intractable diarrhoea and also trophic lesions *The most conspicuous complaint consisted in pain in the* legs which is dull, burning, bursting, tearing, or stabbing in character Sometimes the skin of the legs was hypersensitive, and the patient was not able to endure the weight of the bedclothes Dysaesthesiae were very frequent, particularly of a disagreeable sort, worse at night No fewer than 20 patients (i e , 13 3 per cent) sought medical help because of trophic lesions Foot-drop and other forms of paresis, and also ataxia, were rare complaints.

On physical examination, the commonest sign consisted in loss of the ankle jerks (80 per cent), the knee jerks being unobtainable (on one side or both) in about one-third In three-quarters of the series, disorders of superficial sensibility were demonstrable. Vibration sense was lost in two-thirds, and postural sensibility in the toes in nearly 28 per cent. Tenderness of the muscles or of the *tendo achillis* was not a reliable diagnostic test Paralysis of the arm was seen only 3 times, as opposed to 12 instances where there was partial or complete foot-drop Cranial nerve palsies were not common, though perhaps more frequently encountered than in the general population

This may perhaps be evidence of intracranial vascular degeneration and not of cranial polyneuritis. Pupillary anomalies were met with in 13 patients (9 per cent) and included sluggish or inactive responses to light. True Argyll-Robertson pupils were found in two patients. Examination of the cerebrospinal fluid was carried out in only 26 patients from this series, and from these, 10 fluids showed a protein level above 45 mg /100 ml., the highest figure being 160. There did not seem to be any parallelism between the severity of the nerve involvement and the protein level in the cerebrospinal fluid.

Oedema of the ankles occurred in one-third of the patients It was common to note anhidrosis of the feet, atrophy of the skin, and malformed or pigmented toenails. In 20 cases, tests of the efficiency of the vasomotor and sudomotor nerves to the legs were carried out, with evidence of impairment in every one. Two types of response were found: in one-half there seemed to be a vasoconstrictor paralysis. In the other half, the legs remained cold despite heating of the trunk Recurrent attacks of nocturnal diarrhoea occurred in 27 patients (18 per cent) Disturbed control of the act of micturition was met with in 12 cases Sexual impotence was found in 38 out of 70 male patients (54 per cent), some of the subjects being young adults. In all those with impotence, the bulbo-cavernosus reflex was absent. Neuropathic foot lesions, including perforating ulcers, occurred in 18 patients Bone and joint lesions occurred in 9 subjects (i.e , 6 per cent). Charcot arthropathies were found to develop rapidly in some cases of diabetic neuropathy.

Out of the series of 150 cases, 50 patients (33 per cent) also showed diabetic retinal disease with haemorrhages and exudates. It was considered, however, that retinal changes in diabetics are related mainly to the duration of the disease The association of diabetic peripheral nerve disease and the so-called Kimmelstiel-Wilson syndrome of nephropathy seemed to be co-incidental Diabetic neuropathy, apparently, was mainly related to diabetic neglect, while retinopathy and nephropathy are associated more clearly with the duration of the disease

The author went on to examine the views commonly held as to the aetiology of diabetic neuropathy The three most popular conceptions comprise the notion (a) that neuropathy is attributable to peripheral degenerative vascular disease, (b) that it is the expression of a vitamin deficiency, and (c) that it is directly a result of a disordered metabolism Detailed reasons are given in this article for the third of these hypotheses, namely that neuropathy is to be associated with diabetes directly Neither ketosis nor coma seem to be directly related Though prolonged neglect of a state of diabetes is a potent factor in the aetiology of neuropathy, so too, apparently, is the factor of rapid establishment of diabetic control [the "insulin neuritis" of Caravati (36)] The cases of two patients are quoted where nondiabetic hyperglycaemia, due respectively to acromegaly and to haemochromatosis, was associated with a peripheral neuropathy Martin concludes that nerve involvement of some degree is very common in diabetics, the margin of safety being

slender. Only by exercising care with a diabetic and insulin regime can the diabetic escape from serious neuropathy.

Diabetic myelopathy has recently been studied by Garland & Taverner (37), who referred to relevant findings reported over 60 years ago by Bruns (38). Their series was made up of five patients whose ages extended from 53 to 76 years All had diabetes of rather short duration, untreated with insulin. The neurological picture comprised asymmetrical pain in the legs, weakness and wasting of the muscles of the legs, and loss of knee and ankle jerks. There was no objective sensory impairment. Examination of the cerebrospinal fluid showed a high protein content (34, 105, 109, 120, and 139 mg / 100 ml). The authors based their diagnosis of a spinal rather than a peripheral origin upon the frequent presence of extensor plantar responses, and upon electromyographic changes which were characteristic of a myelopathy.

Arthropathies, painless in type, are well-known to occur in diabetics, resembling the Charcot joints of patients with tabes and with syringomyelia. Bailey & Root (39) have studied this particular complication, and out of a population of about 20,000 diabetics they were able to collect 17 cases In each instance, the arthropathy involved the foot. The earliest gross change, according to these authors, consists in a thickening of the tarsal region There is no increase in synovial fluid The swelling is painless, and without any redness of the overlying skin, or heat, or any other evidence of inflammation Gradually there develops a thickened and deformed foot, with a tendency towards eversion and external rotation and a flattening of the longitudinal arch The skiagraphic appearance is very like that of a tabetic arthropathy though the bony changes are more limited in their extent It is not always easy to distinguish clinically or radiologically the two conditions. In the tabetic cases there may occur an acute and temporarily painful increase in fluid within the tarsal joints Formation of new bone is more characteristic of the tabetic cases The authors did not consider that the diabetic arthropathies were secondary to peripheral ischaemia Of their 17 cases, 14 showed other evidences of neuropathy, a condition which they considered to be of aetiological significance

Localized muscular atrophy—It is common knowledge that injections of insulin may be followed by atrophic changes around the site of puncture. Less well known is the fact that similar types of atrophy may occur in diabetics who have not been receiving insulin at all Although rarely identified as such, this kind of atrophy has been known since the original observation of Bernard & Féré (40) Six of these cases have been described by Hirson (41), all in females, their ages ranging from 46 to 76. Unlike the condition known as local panatrophy, the overlying skin was not affected in these cases. The atrophy was found in unusual sites for injection purposes

Neurological Complications of Carcinoma

There is an increasing realisation that unexpected complications referable to the central nervous system may develop in patients with inoperable can-

cer, in the absence of any direct involvement with metastases. They may be divided into two main syndromes: namely, a picture of cerebellar atrophy and, secondly, a polyneuritis.

The development of a variety of subacute cerebellar degeneration in cancerous patients seems to have first been noted in an accidental fashion as it were, and it was many years before the role of the associated carcinoma was realized to be significant and not coincidental. Thus, some of the earliest cases were published merely as examples of a cerebellar atrophy of "delayed," "presenile," or obscure nonfamilial type. Only later did neurologists tumble to the conclusion that they were in the presence of a correlation, which, however unexpected or mysterious, was none the less statistically significant. Priority would seem to belong to Lhermitte, perhaps the greatest of living neurologists. In 1922 he wrote a paper upon astasia-abasia resulting from atrophy of the cerebellar vermis in aged or elderly subjects (42). One of his patients was a man of 67 years who died from a carcinoma of the pancreas. No aetiological relationship was claimed here. Seven years later Casper (43) wrote up the case of a woman with cancer of the breast who developed a chronic cerebellar syndrome. Next, in chronological order, comes the paper written by Parker & Kernohan (44) dealing with the problem of chronic atrophy of the Purkinje cells and read before the Chicago Neurological Society. Their patient was a woman of 58 years who began to develop a progressive weakness of the limbs, loss in weight, and depression, a little less than two years before. Her condition deteriorated. She was regarded as suffering from a progressive cerebellar degeneration, and her decline was ascribed to a large pelvic tumour and to active phthisis. She lived for a period of 27 months from the presumed date of onset of the neurological features. At autopsy a condition of cerebellar atrophy was found and, in addition, there was a healed tuberculous lesion in the lungs, together with a bilateral carcinoma of the ovaries with metastases in the liver and lungs, and extension to numerous lymphatic glands. Then came Greenfield's paper dealing with subacute spino-cerebellar atrophy in elderly patients (45). Two cases were described, both differing from the better known types of cerebellar degeneration which appear late in life, namely, olivo-ponto-cerebellar atrophy [Dejerine & André-Thomas (46)] and parenchymatous cortical cerebellar atrophy [Marie, Foix & Alajouanine (47)].

It is quite obvious, in retrospect, that these writers had erred in focussing their attention upon the dominant cerebellar picture, and, in an effort to align their cases with other examples of cerebellar degeneration of late appearance, they glossed over or ignored the concomitant carcinoma. In this respect they seem badly to have missed the bus; that is, if our present day ideas should turn out to be as valid as they appear just now.

A further paper by Greenfield, in collaboration with Brain & Daniel (48), gave the first explicit attempt to link the two conditions of carcinoma and subacute cortical cerebellar degeneration. Four cases were quoted of cerebellar disease occurring fairly rapidly in subjects past middle age, who

succumbed at the end of periods varying from 7 months to 3½ years Autopsy revealed diffuse degeneration of the cerebellar cortex and, in three, degeneration of one or more of the long tracts of the spinal cord also In these three cases there was also cancer present, in the lung in two and in the ovary in the third Among the clinical symptoms, the authors drew attention to the early appearance of pain in the legs and of mental deterioration The cerebrospinal fluid showed excess of cells and protein in the three cases associated with carcinoma In one of these a strong Lange reaction of paretic type was also present The authors were at a loss to identify the mechanism which links carcinoma (especially of the lung or of the ovary) with subacute cerebellar degeneration. There is no evidence of any specific alteration of bodily metabolism. The authors were fully aware of the fact that the Purkinje cells seem to be sensitive or vulnerable structures, liable to be implicated by various toxic and infective agencies Later studies of this clinical association include the papers by Barraquer-Bordas & Lowenthal (49) and by Henson, Russell & Wilkinson (50).

The polyneuritic picture is anything but a simple one, and it is quite possible that a number of clinical sub-types really exist. Heathfield & Williams (51) isolated a sensory neuropathy, a mixed sensori-motor neuropathy, and a myopathy. Whether this classification errs by being too mutually exclusive and too rigid, time will no doubt show

Parkes Weber & Hill (52) were among the first (if not indeed the actual pioneers) to report a polyneuritis in association with carcinomatosis. The patient was a man of 39 years who, while convalescent from pneumonia, developed a peripheral neuritis. His condition steadily deteriorated, and he died about a year after the original infection Post-mortem examination revealed extensive malignant disease in both lungs, pancreas, suprarenals, liver, kidneys, spleen, vertebral column, parotid gland, and the retroperitoneal lymph glands Examination of the spinal cord showed degeneration of the posterior columns Unfortunately the peripheral nervous system was not studied, but the authors deemed it safe to conclude from their clinical data that a peripheral neuropathy must have been present. The authors referred to the belief that a polyneuritis might develop on the basis of a carcinomatous cachexia

Other papers have since appeared in which a clinical condition of polyneuritis (or peripheral neuropathy) has arisen in cancerous subjects [Lennox & Prichard (53), Wyburn-Mason (54), Kremer & Pratt (55), Elkington (56); Henson (57), Henson, Russell & Wilkinson (50), Heathfield & Williams (51)] From the evidence available it appears that the symptoms develop gradually and progress slowly Remissions may occur Examination shows sensory ataxia, areflexia, and a radicular type of impaired sensibility Subjective symptoms include pains, cramps and tenderness of the muscles, which may be very intense Troublesome burning feelings in the feet are also present If the clinical manifestations remain at this stage, we have the picture which is often spoken of as "primary sensory neuropathy" The first case recorded

cer, in the absence of any direct involvement with metastases They may be divided into two main syndromes: namely, a picture of cerebellar atrophy and, secondly, a polyneuritis.

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clinically was shown at a medical society meeting by Kendall (58). Later this patient died, and the pathological findings were studied in great detail, with one other case, by Denny-Brown (59). [The same two patients and one other have also been the subject of a paper by Wyburn-Mason (54), an unfortunate example of reiterated case reporting.] Both cases had a bronchogenic carcinoma. The posterior columns of the spinal cord were degenerated, as were the dorsal nerve roots. The muscles showed a considerable amount of proliferation of connective tissue and sarcolemmal nuclei with swelling of isolated fibers. Denny-Brown (59) regarded the process as a diffuse degenerative one, affecting primarily dorsal root ganglion cells, together with a degeneration of striped, voluntary, muscle fibre. The condition was not the same as the nutritional ataxia met with in the victims of Japanese prisoner of war camps. Both the nervous degeneration and the muscular changes were deemed to be consistent with a metabolic disorder (and resemble the effects of deficiency of pantothenic acid in pigs).

Whether it is logical and correct to separate sharply the purely sensory cases of a carcinomatous neuropathy from those of carcinomatous polyneuritis is debatable. In the literature they are very often distinguished, as though they were two quite different disorders. It seems more likely upon every ground, clinical as well as pathological, that every gradation should occur between cases of neurological complications of cancer, where the posterior columns, the dorsal root ganglia, the peripheral nerve-trunks and the muscles are involved. In some cases the brunt falls evenly upon all these structures; in others the stress is uneven.

The final group includes syndromes which are reminiscent of a primary disease of muscles themselves. Myasthenic and also myotonic-like symptoms *may be demonstrable. The wasting is proximal rather than distal* in distribution The vexed question as to the nature of the lesions is not really solved even by a biopsy. Degenerative changes in the muscle are patchy. Striation is lost; nuclei are increased in number. Walton (60) was inclined to regard these histological changes as being those of a polymyositis, and in turn to equate the "menopausal muscular dystrophy" of Shy & McEachern (61) with a polymyositis Dermatomyositis with malignant disease has also been recorded by Dostrovsky & Sagher (62) and McCombs & MacMahon (63).

The question of causation of the neurological syndromes in carcinomatous patients is still uncertain A chance coincidence is unlikely It is possible that a toxin produced by the cancer operates adversely upon the nervous system. An alternative hypothesis implicates a virus. A nutritional defect, suspected in some of the earlier cases, now seems to be unlikely. It is difficult, however, to escape the suspicion that some biochemical anomaly might be responsible. Denny-Brown (59) wondered whether bronchogenic carcinoma might not produce a by-product (such perhaps as thiopanic acid or phenyl pantothenone) which would interfere with the biological conjugation of pantothenic acid.

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PSYCHIATRY[1]

By Ian Stevenson

Department of Neuropsychiatry, Louisiana State University School of Medicine, New Orleans, Louisiana

Introduction

No major advances in psychiatry occurred during the past year. However, a number of individual contributions demonstrate gradual progress in the field and carry the promise of even greater achievements Viewed over a longer period than is covered by this review, the psychiatric literature shows signs of a slow change towards more mature research and reporting. The development of modern psychiatry was accompanied by luxuriant speculation in which fancy so far outran the facts as to bring justified censure on the specialty from other branches of medicine (1). Now, both from increased wisdom and greater necessity, psychiatrists are applying themselves more and more to the less exciting and more exacting labor of gathering facts

Experimental Psychoses

Some recent developments in the experimental psychoses warrant a brief survey of this subject For many years psychologists and psychiatrists have known a number of substances capable of producing temporary psychoses Mescaline, (derived originally from the cactus *Anhelonium lewinii* and later synthesized), has been known to have such properties since the last century Between 1925 and 1940 the mescaline psychosis was studied extensively, especially in Germany and Great Britain Bulbocapnine and kindred substances have likewise been known for many years to produce catatonic-like phenomena in animals (2) In 1943, an alkaloid of the ergot group (*d*-lysergic acid diethylamide tartrate) was accidentally found capable of inducing a transient psychosis (3). This discovery further stimulated the study of the experimental psychoses Many detailed reports of the effect of mescaline and *d*-lysergic acid on normal and schizophrenic subjects have since been published (4 to 8)

A major difficulty in relating the experimental to the natural psychoses lay in the fact that of all the substances known to produce psychoses artificially, none was a naturally occurring substance of the human body. The demonstration of a toxic substance or substances in the sera of schizophrenic patients (9, 10) encouraged the search for a naturally occurring substance capable of producing psychoses In 1952, Osmond & Smythies (11) published a review of the similarities between schizophrenia and the mescaline psychosis In this paper they drew attention to the similarity between the structural formula of mescaline and that of epinephrine (Fig. 1) They postulated that a perversion of the metabolism of epinephrine might result in the production

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phrenia may turn out to be a group of somewhat similar disorders having different origins Some authors are already calling for distinctions within the group of schizophrenic-like psychoses (13) It may be found that some schizophrenic-like psychoses have a toxic origin, and others do not. In any case, the study of the experimental psychoses has now come closer than ever before to improving our understanding of the natural psychoses.

Psychopathology

Studies by Johnson and her colleagues (14, 15, 16) have contributed new and useful insights into the problem of fixations in children and antisocial behavior in children and adults Before describing their conclusions, attention should be drawn to their excellent method of study. They observed simultaneously (in therapy) both the child with the presenting symptoms and one parent The parent and the child were treated by different therapists, but the therapists collaborated in their treatments of the patients This technique improved on the reconstruction at second-hand of the psychodynamics of the parent from the study of the child. The authors report experiences with this method extending over a period of 12 years The length of the study, the evident carefulness with which it has been conducted, and the special features of the method, all evoke respect for the conclusions drawn by these authors

From this study of the interaction of parents and children, Johnson and her colleagues conclude that fixations and antisocial behavior in children express some uncontrolled impulse (often unconscious) in the parent The parent usually covertly, rarely openly, encourages or condones the particular fixation or antisocial behavior Thus the impulses of the parent find vicarious expression in the behavior of the child. Treatment of the child is often useless without treatment of the involved parent

Hitherto, antisocial acting out in children and adults has often been viewed (in the psychoanalytic school) as expressing a need for punishment to assuage an excessive sense of guilt According to this formulation, the child wishes (usually unconsciously) to be punished in order to relieve his sense of guilt. So he does something which will be detected and punished The sense of guilt may be displaced from some other real or imagined offense with which he has charged himself Johnson and her colleagues formulate antisocial behavior differently. They believe antisocial behavior arises only when there is prompting from a parent. (The child may indeed facilitate his own detection so that strong controls will be applied and prevent his doing anything worse) In short, the child suffers not from an excessive conscience, but from a deficient one. And it is deficient, because the parent has lacked the strength to direct the child firmly because of her (or his) own imperfect controls Sometimes such a chain of defective controls could be traced back through the parents to the grandparents and thus observed in three generations Mowrer has similarly recently emphasized the role of imperfect conscience function in many neuroses (17).

of a substance somewhat similar to mescaline and having its toxic properties. Such a substance, they speculated, would be liberated in greater amounts during stress and, if the amount were sufficient, might induce a psychosis such as schizophrenia Working with this hypothesis, Hoffer, Osmond & Smythies (12) have found that adrenochrome, an oxidation product of epinephrine (Fig. 1), also produces psychoses in humans. Adrenochrome is almost certainly, although not definitely, a naturally occurring substance of the human body. It comes closer than any other drug thus far studied to fulfilling the criteria of a toxic substance capable of producing schizophrenia

Many difficulties in this area remain. For one thing the experimental psychoses resemble schizophrenia in some features, but not in all The experimental psychoses are characterized, like schizophrenia, by alterations in perception, intellection, and emotion without impairment of consciousness

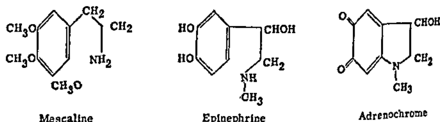


FIG. 1. A comparison of the structural formulae of mescaline, epinephrine, and adrenochrome.

However, disturbances of perception are in the foreground in the experimental psychoses and disturbances of thinking (a major feature of schizophrenia) are relatively minor Visual illusions and hallucinations are a prominent feature of the mescaline psychosis, but auditory hallucinations occur much less frequently In contrast, in adult schizophrenia, auditory hallucinations occur frequently and visual hallucinations rarely. Moreover, some schizophrenic patients have apparently been able to distinguish hallucinations induced by mescaline from their "natural" hallucinations. This would suggest different mechanisms in the experimental and natural psychoses On the other hand, strict identity of phenomena between experimental psychosis (in a normal person) and schizophrenia should not be expected The normal person in the throes of an experimental psychosis is fortified, unless (as happens rarely) he loses insight, by the knowledge that his condition is temporary. No such comforting thought solaces a patient as he first encounters the perceptual distortions of schizophrenia. Naturally he has a much greater anxiety in such an experience To the primary action of a hypothetical toxin would then be added the secondary disorganization produced by the patient's reaction to his changed perceptions (8)

Further research will undoubtedly clarify some of the differences between the experimental psychoses and schizophrenia What we now call schizo-

He reiterates his conviction that the essence of psychoanalytic therapy is a corrective emotional experience for the patient According to this view, in *childhood the patient undergoes certain thwarting or distorting experiences* with his parents. He adapts to life with his parents, but as he grows older, he inappropriately carries these adaptations over into his behavior with other, different persons. Such inappropriate behavior impairs his relations with other people, bringing attendant disturbances of feelings and thought. When the patient comes to the therapist, he at first continues to behave towards *the therapist as if the therapist were going to behave towards him as did his* parents The therapist, however, does not do this He adopts an interested, constructive, and accepting attitude towards the patient The patient gradually learns to respond to the therapist with behavior appropriate to the therapist's behavior Eventually he completely discards the old patterns which were useful and perhaps necessary with his parents, but which are no *longer adaptive*

In this paper Alexander pleads for a more receptive attitude towards innovations in psychotherapy Referring to the heated opposition encountered by modifications which he and his colleagues introduced, he makes a memorable rejoinder which deserves quotation.

> Only time will tell the practical usefulness of these variations One thing is certain, the mere repetition of routine—and the rejection of new suggestions as a threat to the purity of psychoanalysis—can lead only to stagnation Further improvements of technique can come only from a persistent re-examination of our theoretical premises and from relentless experimentation with technical modifications

Three other books published during the period under review further emphasize *psychotherapy as a corrective emotional experience* Rosen has collected a group of previous articles on the psychotherapy of schizophrenia and reprinted them under the title of *Direct Analysis* (22) The structure of the book (a collection of reprints) leaves the reader dissatisfied with the absence of a coherent presentation of the author's views Nevertheless, his therapeutic strategy is clear enough Rosen apparently attributes his success in treating schizophrenia *to his almost surgical boldness in confronting the* patient with the symbolic meaning of his behavior This must play its part in the eventual outcome. However, other features of Rosen's technique may be equally important. For example, he devotes a great deal of time to his patients, often spending from 6 to 10 hr a day with one patient. Moreover, he apparently approaches his patients with an intense and communicated affection His relationships with patients seem to echo what Alexander describes in his work with neurotic patients

The same theme is repeated in *The Roots of Psychotherapy* by Whitaker & Malone (23) These authors insist that psychotherapy is and should be an emotional experience for the therapist as well as for the patient They destroy the stereotype of the psychotherapist as the detached and objective micros-

Therapy

Psychotherapy.—The first volume of Ernest Jones' *The Life and Work of Sigmund Freud* appeared at the end of 1953 (18). No one could perform better than Jones the difficult task of writing the "official" life of Freud. He is the only living member of the original "committee" which gathered around Freud in the early years of this century. Not by age alone, but by ability and experience, he is the dean of all psychoanalysts. In addition, Jones is, like Freud himself, a literary craftsman of the first order. These assets have produced an authentic and a remarkably readable biography. It recounts with great clarity the story of Freud's background, his intellectual growth, and the development of his early psychological theories. But Freud is depicted "warts and all." Fully revealed are the many obstacles in his own personality with which Freud contended. In his early life, he suffered from a wide variety of phobias, depressions, anxiety attacks, and hypochondriacal preoccupations He exhibited, but perhaps did not suffer from, powerful ambition, especially for originality of discovery. This exposition of Freud's struggles with himself, which he never sought to conceal, may serve a double purpose. Certainly the moral courage and integrity with which Freud finally triumphed over both the vexations within himself and the hostility of the professional world furnish splendid inspiration to our generation. At the same time thoughtful psychiatrists, reminded of Freud's background and of his personal imperfections, will also remember a basic principle of psychology which Freud himself taught, but often forgot in evaluating his own theories The principle is simply that "our way of looking at things is conditioned by what we are" (19). And human frailties confer a frailty on human theories

As time has passed, Freud's theories have been extensively criticized and revised both within and without the psychoanalytic movement. An observer cannot avoid noticing that different psychotherapists subscribing to quite different theories of psychotherapy, claim equally effective results We have no grounds for believing that any are dishonest in their claims They may be deluding themselves, but we are not entitled to believe that one group deludes itself more than another. We can only conclude, therefore, that no theory of psychotherapy has as yet adequately captured in words just what the person undergoing psychotherapy experiences

That psychotherapy should be, however, a special kind of emotional experience, seems to be an opinion towards which recent writings on the subject converge For many years emphasis in psychotherapy has been placed, at least in the literature of psychoanalysis, on the recovery of forgotten memories and the achievement of verbalized insight as means towards recovery. This view has been gradually displaced by descriptions of psychotherapy as an educative or re-educative emotional experience for the patient. Alexander and his associates have emphasized this for some years (20). A sample only of current writings on this subject can be considered here

Alexander has contributed a review of his theory of psychotherapy (21)

with 19 "unimproved." Unfortunately, his study included no control group. Hargrove and his colleagues (30) compared the results of treatment with carbon dioxide therapy and with psychotherapy in two groups of comparable patients. They observed more favorable results with psychotherapy alone and found a large number of abreactions which were disturbing to the patient and difficult for the therapist to handle. In this study, however, they did not use the method recommended and found valuable by Meduna. From a detailed review of cases reported in the literature, Frank (31) concluded that carbon dioxide therapy "may be a useful adjunct to psychotherapy" and "is capable of causing amelioration of some neurotic symptoms without the use of concurrent psychotherapy." Meduna (32) contributed a revised version of the theory on which he bases the use of carbon dioxide therapy This theory chiefly supposes the interruption by carbon dioxide of reverberating inhibitory circuits in the central nervous system. Meduna offers a purely physiological theory. He ignores the psychologic impact which giving a gas to the point of unconsciousness must have on any patient. And there are many other psychologic ingredients in this treatment, such as the repeated personal, even if brief, contacts with the therapist, the enthusiasm of the therapist for the treatment, and his solicitude for the patient's recovery. These factors no less than the physiological effects, must be acknowledged in any satisfactory theory of carbon dioxide therapy.

The foregoing papers on carbon dioxide therapy permit no final statement about its usefulness Much further study, especially with careful control, is needed. Almost certainly, carbon dioxide does not have a specific action in the psychoneuroses, as Meduna has claimed Equally certainly, it does have some beneficial effect in many patients It does not seem rash to predict that carbon dioxide therapy, even when the initial enthusiasm has relaxed, will have some place in psychiatric treatment. Indeed it may be said already to be established as a helpful aid to psychotherapy. Carbon dioxide treatments can often permit a patient to abreact experiences or express feelings more rapidly than he could do without this help. Patients who are hostile to psychotherapy and receptive only to a physical therapy will often accept carbon dioxide therapy (31). Then, through the abreactions induced, they may be led to participate actively in psychotherapy. And finally, carbon dioxide therapy seems to have, in some patients, a definite capacity for reducing the level of physical tension even in the absence of remembered abreaction.

Other pharmacologic therapies.—The treatment of schizophrenia remains quite inadequate Psychotherapy has demonstrated value, but many factors limit its applicability. It takes a great deal of time, and there are relatively few practitioners Many patients obtain some psychotherapeutic benefit from association with other patients and with the staff in the community of a hospital Others, however, are cut off from even this assistance because their excessive motor activity obliges the personnel of the hospital to restrain, seclude, or sedate them. When any of these measures are applied, the pa-

copist of the patient's dilemma. Rather the therapist is exhorted to share at the appropriate time his own feelings and thoughts with the patient. The importance of emotional participation by the therapist has been the subject of other recent contributions (24, 25).

Still another exposition of the same principle is provided by the work of Dr. Maxwell Jones and his associates at the Industrial Neurosis Unit of the Belmont Hospital, London. Their methods are presented in *The Therapeutic Community* (26). The title of this book expresses the aims of its authors The patients of the program described, all of whom have severely disabling neuroses or psychopathic personalities, live together with the staff in a community within the larger hospital. Individual psychotherapy leading to verbalized insight has a minor role in the program. Instead emphasis is placed on the training (or acculturation) of the patient by the community. The community, by virtue of the presence in it of the staff and of the senior patients, is always healthier in its responses than the newly arrived patients. The latter, as they interact with the other members of the community, gradually learn and practice more mature responses first within the community and then outside it. Emotional and corrective interaction occurs in day-to-day living and in therapeutic group meetings. Vocational rehabilitation is stressed in the program. There are opportunities for work at various manual trades The patient, almost from his admission to the unit, is guided and counseled toward suitable employment at the time of his discharge. The program relies much on the contribution to the community of nurses who are sociable and kindly, but technically untrained. Thus a small number of psychiatrists can supervise the treatment of a much larger number of patients than is ordinarily possible. The immediate results of this program have been excellent Unfortunately, the published report gives follow-up studies extending only six months after discharge.

Another noteworthy literary event of the period under review was the publication of the first volumes of *The Collected Works of C. G Jung* The first of the series, *Psychology and Alchemy* (27), was issued in 1953 Two others have since followed and more will appear over the next few years Jung's theories have hitherto been less well known in the United States than those of Freud In Europe, on the other hand, Jung commands an equal or greater respect than Freud, and his influence increases His relative neglect in this country may be in part the result of the fact that many of his works have been out of print or never translated. Now this deficiency is to be remedied and students of Jung will have up to date editions of his work.

Carbon dioxide therapy.—Since the appearance of Meduna's book *Carbon Dioxide Therapy* (28) in 1950, psychiatrists have shown considerable interest in this method of treatment Studies have been made by authors seeking to confirm the favorable results reported by Meduna A number of such evaluations were reported during the period of this review Moriarty reported favorable results in combined psychotherapy and carbon dioxide therapy (29). He found 42 of 100 patients "much improved" and 39 "improved,"

which again removes him from the opportunity for research. Kubie proposes the formation of psychiatric research institutes in which research would be conducted by qualified psychiatrists with little interference from other demands for their services This suggestion, although meritorious, is a fantasy not likely to be realized in the near future But Kubie's article provides a timely and well-reasoned study of an urgent problem

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tient is even more isolated than before from the beneficial effects of contact with other persons. Electro-shock therapy will reduce excessive motor activity, but often at the cost of interfering with the patient's memory and other integrating functions. For these reasons psychiatrists would welcome drugs which can reduce motor activity without interfering with memory or reducing the level of consciousness

Two such drugs are now being studied and may prove valuable themselves or the forerunners of the ideal drug. *Rauwolfia serpentina* has been used in the Ayurvedic medicine of India for centuries. It has received extensive interest recently because of its hypotensive action and its use in the treatment of hypertension. References to its use in various psychiatric conditions occur in the Indian medical literature. Kline and his colleagues (33) undertook an extensive and controlled study of the sedative action of *Rauwolfia serpentina* on psychotic patients in a hospital They found a definite sedative action, but concluded that since such effects were not invariable, much more study is needed to determine for which patients this drug will be a useful sedative.

Chlorpromazine hydrochloride, after development in France, has been introduced in this continent and used to reduce excessive motor activity in psychiatric patients (34, 35). This substance is a chlorinated phenothiazine. It inhibits both sympathetic and parasympathetic activity, being primarily a ganglioplegic. It is also a sedative, but has a relatively greater action on motor activity than on levels of consciousness It can therefore be used in excitable and hyperactive patients in whom it will reduce motor activity with relatively little associated drowsiness or sleep. Further study of this drug also is needed, but the preliminary results of its use are encouraging

THE SUPPORT AND PLANNING OF RESEARCH

As mentioned in the introduction to this review, psychiatrists are showing greater interest in organized research into the problems of the specialty. Those who wish to do research frequently meet many difficulties before they can carry out their intentions There is a serious shortage of funds available for psychiatric research and a shortage also of persons qualified to carry it out Kubie (36) has reviewed the second aspect of the problem, the shortage of trained research workers in psychiatry. The psychiatrist today must undergo a long period of training and maturation to qualify himself for the difficulties of his specialty. During the period of training his creativity may be restricted by the demands of the training program and by the conflicting interests of his superiors After he has completed his training, other factors limit the opportunities for research. Organized (which means effective) research requires much financial support Nowadays such support is hardly to [illegible] medical

DISEASES OF THE RESPIRATORY SYSTEM[1,2]

INTERPRETATIONS OF TESTS OF FUNCTION

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INTRODUCTION

The lungs are perfectly designed to fulfill their function of ensuring full oxygenation of the blood and they achieve this by possession of the following properties (*a*) The distensibility and elasticity of the lungs enables a large volume of gas to be moved in and out of the alveoli at a rapid rate and with minimal effort. (*b*) Gas drawn into the lungs is distributed almost evenly to all alveoli and the blood perfusing the lungs goes equally to all parts. (*c*) The alveolar membrane is so fine that gas diffusion through it is very rapid (*d*) The very large alveolar surface (ca 55 sq m) and the relatively small volume of blood contained within the alveolar capillaries (ca 60 cc.) ensures the saturation with oxygen of blood passing through the lungs (*e*) The pulmonary vascular bed can accommodate a considerable increase of blood flow without a corresponding increase in pulmonary arterial pressure

It might be thought that such detailed knowledge of the attributes of the normal lung would have led to the development of tests precise enough to measure quantitively all the various disturbances of function that occur in disease This is not the case One of the reasons for this state of affairs is the difficulty in assessing the normality of one function in the presence of impairment of others Another is that the methods of investigation are often technically difficult to perform and until the introduction of rapid physical methods of gas analysis, the tests of most value were often extremely time consuming

Pulmonary function tests are concerned with the first three of the attributes of normal lung function detailed above, and may be conveniently considered under the following headings (*a*) the mechanical efficiency of breathing and the subdivisions of lung volume, (*b*) measurements of the uniformity of gas distribution within the lungs, (*c*) measurements of the efficiency of haemo-respiratory exchange

In this review, an attempt is made to assess the clinical value of some of these tests, although in our opinion their main value is in research In general,

[1] The survey of literature pertaining to this review was completed in April, 1954

[2] The following abbreviations are used in this chapter ACTH (corticotropin), M.V.V (maximal ventilatory volume)

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closed circuit methods are generally preferred to the open circuit nitrogen technique, since they are quicker to perform, and the continuous respiratory tracing enables a correction to be made easily for any error in the "switch in point" Using a helium circuit Gilson & Hugh-Jones (9) found the standard deviation of duplicate determinations to be about 60 cc., and our experience has been similar to this. We have not found the larger variation reported by Whitfield (10) There is no reason why the helium closed circuit and the nitrogen washout methods should give different values (9), and the explanation of some of the differences in the literature is probably to be found in the posture of the subject while the determination was being performed. Although the functional residual capacity (FRC) is often increased strikingly in emphysema, by itself it has no absolute diagnostic value. The balance of forces that control the level of the FRC in any one subject is not yet easily measurable in a quantitative manner, and it is still difficult to assess precisely the meaning of changes in the FRC Although it characteristically increases in the presence of bronchospasm, we have studied exceptions to this rule There is no evidence that progressive clinical deterioration in emphysema is closely paralleled by an increasing FRC, though this many be observed in some cases (2)

Composite Ventilatory Indices

A number of indices of function based on ventilatory measurements have been proposed, and some of these have been credited with considerable value in diagnosis Most of the claims that have been made for them, however, can be shown to be fallacious in particular cases, and, in some instances, when detailed figures are given (11), it is evident that the index is unlikely to be more sensitive than its component parts The index

$$\frac{(\text{M V V} - \text{Resting Min Vol})}{\text{M V V}} \times 100$$

has been introduced by Cournand and Richards as an index of dyspnoea. Ornstein *et al* (11) have proposed a variant of this in which the M V V. is divided by the resting minute volume In many conditions the resting minute volume is not abnormal, however, and there seems little to be gained from adding or substracting it from other measured volumes We agree with Comroe (12) that these and similar indices are of little value The effect of increasing age on ventilatory function is occasionally ignored and good discrimination has been claimed for some indices between young normal subjects aged about 20 years, and cases of emphysema in middle age (13)

The residual capacity expressed as a percentage of total lung volume has been generally used in assessing respiratory function This percentage is found to be raised considerably in emphysema since in this condition the residual capacity is customarily increased and the vital capacity is reduced It is usually increased in asthma for the same reason The fraction is often

little attention has been paid to technical details, since many of these have recently been described elsewhere (1) and usually individual authors have described their own techniques in full.

THE MECHANICAL EFFICIENCY OF BREATHING AND THE SUBDIVISIONS OF LUNG VOLUME

THE VITAL CAPACITY

This, the oldest and simplest of the tests of pulmonary function, is now little used by itself as an indication of pulmonary disability The overlap between normal and abnormal is considerable and usually abnormality is clinically obvious before the vital capacity indicates a deviation from normal values that is unequivocal In our experience the vital capacity is not necessarily related to disability in a variety of diseases, and in emphysema it gives no indication of severity, nor is clinical deterioration inevitably accompanied by a change in the vital capacity (2) Much work has been done on the calculation of ventilatory indices from the record of a fast vital capacity measurement on a rapid kymograph (3, 4), and it seems likely that an index based on this procedure provides a fairly reliable indication of the M V.V.[2] It is not yet clear whether it reveals information in any sense additional to it. Lowell (5) has studied the rate of change of gas flow and notes that this is very variable in patients with lung disease during the course of a single expiration Bernstein (6) has recently critically reviewed the technique of recording a fast expiration and produces evidence that some of the alleged physiological variations in the reported tracings are mechanical artefacts

THE MAXIMAL VENTILATORY VOLUME (M.V.V.)

Although this is a simple measurement, it is subject to error and variation for two reasons Firstly, the spirometer used to record the inspiratory tracing may interfere with the measurement by lag and overswing, as pointed out by D'Silva & Mendel (7), and secondly, the performance of the test is said to be influenced by the respiratory rate at which it is performed (8) The first difficulty can be overcome by the use of a light weight spirometer bell or by using Douglas bags The second is less easy to surmount and may account for the wide day to day variation in individual subjects noted by Comroe (1) An additional difficulty is that its performance does not exactly parallel the ventilatory increase on maximal exercise, since at rest much higher positive intrathoracic pressures are developed than during exercise Further, it is clear that the sensation of exertional dyspnoea is not necessarily directly linked with a reduction in the M V V Considerable care must therefore be exercised in the interpretation of the significance of this measurement

SUBDIVISIONS OF LUNG VOLUME

The determination of the functional residual capacity requires rather more elaborate apparatus than the M.V V or vital capacity. In Europe

of this work is expended on the elastic resistance of the lungs and how much on the viscous or nonelastic resistance (20 to 24).

The measurement of intrathoracic pressure is a simple procedure; a fine polythene tube is swallowed and the intraoesophageal pressure which has been shown to be the same as the intrapleural pressure, is recorded (25, 26). From measurements of this kind it appears that, on exercise, the limit of respiratory effort is reached when with each breath the subject has to exert a force of about 40 cm of water on the lungs in order to maintain ventilation according to the demands of exercise (19). A patient with mitral stenosis or emphysema who reaches his limit of respiratory effort when breathing 20 or 30 l a min. may be exerting the same force on his lung as a normal individual who is breathing 100 l a min. The reason for this is quite simple More force is required to distend the lung, in the case of mitral stenosis, because the lung is congested and rigid, and, in the case of emphysema, because there is an increase in viscous or nonelastic resistance

If the thesis be accepted that patients with excessive dyspnoea on exertion are short of breath because more force is required to distend the lung, *the way is clear to assess this symptom objectively by simultaneous measure*ments of tidal air and intrathoracic pressure while the patient is exercising This approach is, however, still in the experimental stage

MEASUREMENTS OF GAS DISTRIBUTION WITHIN THE LUNGS

A number of different techniques have been described for the measurement of the efficiency of gas mixing in the lung The first practicable clinical method to be described was the nitrogen washout technique of Darling *et al.* (27) This possesses the advantage of simplicity, but since no correction is made for difference in lung volume and minute volume, this index is relatively insensitive to abnormal gas distribution, particularly in cases where hyperventilation is associated with a small functional residual capacity This limitation has been clearly recognized by some authors (28) but by others it has been disregarded. The estimation of changing nitrogen concentration during a prolonged expiration provides a simple, rapid, and sensitive index of impaired gas mixing (29, 30) but requires rapid gas analysis equipment for its performance. In Europe closed circuit methods are generally used, and indices of mixing derived from these circuits are quickly obtained and are sensitive enough for routine clinical investigation The method suffers from the disadvantage that some discrimination is lost as no correction is made for the respiratory dead space, though this is not an important consideration in most circumstances Another minor disadvantage is that the calculation of the theroetical number of breaths for a given stage of equilibration is dependent on the volume of the individual circuit used There is little doubt that the breath by breath open circuit analysis perfected by Fowler and his colleagues (31) is the most complete and precise method of measuring this

raised in cases of thoracic deformity although in this condition the reduction in the vital capacity is accompanied by a small residual capacity. It is slightly increased in the presence of pulmonary congestion for the same reasons. It increases steadily with advancing years as a result of the progressive reduction in vital capacity, and we have found values of over 50 per cent in some elderly normal subjects who have no evidence whatever of lung disease. Although it is true that in established emphysema, values below 50 per cent are rarely encountered, figures above 35 per cent cannot be taken to indicate the presence of emphysema, as has been assumed by some authors (14). The influence of age on the index has been insufficiently appreciated in some work in which young medical students are compared to middle-aged coal miners (15). In general, it is our experience that the ventilatory measurements that compose these indices are better considered separately if confusion is to be avoided.

The Assessment of Dyspnoea

Numerous exercise tolerancetes ts have been designed to measure exertional dyspnoea (16, 17) but whether these give a better assessment of disability than a careful analysis of the patient's activities, is still a matter of opinion. The principal difficulty in the assessment of dyspnoea lies in its definition. To some dyspnoea means the consciousness of the need for further respiratory effort (18), a rather vague sensation which a normal individual experiences on exercise when his metabolic rate has increased six- or seven-fold and his minute volume respired has increased to about 40 l. To others the term dyspnoea means the sensation that the limit of respiratory effort has been reached (19), a sensation which a normal individual experiences with a 10- to 15-fold increase in metabolic rate, when he is breathing about 100 or 120 l. of air a min Whatever definition be adopted, dyspnoea remains a subjective sensation and the final judgement as to its onset or severity lies with the subject who is experiencing it. Its assessment may therefore be profoundly influenced by the stamina of the subject as well as his reaction to the test and other factors

It has been clear for some time that further progress in the assessment of dyspnoea will only be made when an objective measurement of the factors responsible for this symptom is developed Recent investigations on the work performed by the respiratory musculature suggest that objective measurements of the kind required may now be possible On inspiration the pleural or intrathoracic pressure becomes more negative, the fall in pressure being a direct measure of the force exerted on the lungs by the muscles of inspiration If this pressure change and the tidal air are measured simultaneously and are accurately recorded so that there is no significant time lag, it is easy to calculate the amount of work which has to be done by the respiratory muscles in order to distend the lungs. It is also possible to indicate how much

of this work is expended on the elastic resistance of the lungs and how much on the viscous or nonelastic resistance (20 to 24).

The measurement of intrathoracic pressure is a simple procedure; a fine polythene tube is swallowed and the intraoesophageal pressure which has been shown to be the same as the intrapleural pressure, is recorded (25, 26). From measurements of this kind it appears that, on exercise, the limit of respiratory effort is reached when with each breath the subject has to exert a force of about 40 cm of water on the lungs in order to maintain ventilation according to the demands of exercise (19) A patient with mitral stenosis or emphysema who reaches his limit of respiratory effort when breathing 20 or 30 l. a min. may be exerting the same force on his lung as a normal individual who is breathing 100 l. a min The reason for this is quite simple More force is required to distend the lung, in the case of mitral stenosis, because the lung is congested and rigid, and, in the case of emphysema, because there is an increase in viscous or nonelastic resistance.

If the thesis be accepted that patients with excessive dyspnoea on exertion are short of breath because more force is required to distend the lung, the way is clear to assess this symptom objectively by simultaneous measurements of tidal air and intrathoracic pressure while the patient is exercising. This approach is, however, still in the experimental stage

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aspect of lung function, but the labour of the calculation makes it unsuitable for routine work.

Uneven gas distribution within the lungs is caused by a wide variety of conditions. The test is very sensitive to bronchospasm, and it has been shown that it may be grossly abnormal in the absence of auscultatory evidence of bronchospasm in the chest (32, 33). A recent study using Fowler's technique (34) has indicated the difficulties of translating abnormality of gas distribution into precise pathological terms. Uneven gas distribution is not necessarily correlated with impairment of haemo-respiratory exchange, since the first appears to be mainly linked with mechanical factors, and the second is dependent on the efficiency of gas exchange in the lung or with the efficiency with which the abnormal gas distribution has been met by local variations in perfusion and diffusion within the lung

MEASUREMENTS OF THE EFFICIENCY OF HAEMO-RESPIRATORY EXCHANGE

Arterial O_2 Tension

It has been realized for many years that the shape of the oxyhaemoglobin dissociation curve makes variation in oxygen tension a more sensitive index of respiratory function than measurements of oxygen saturation. Only recently, however, have methods of measuring gas tensions in the blood been perfected Bjork *et al* (35) have measured the resting arterial pO_2 in patients with varying degrees of pulmonary tuberculosis, and they find a lowered resting oxygen tension a useful guide to pulmonary reserve This contribution contains some interesting correlations between the arterial pO_2 and the ventilatory tests of function

The "Alveolar-Arterial Gradient"

The pioneer work of Riley, Cournand & Richards (36, 37, 38) has greatly increased the value of measurements of arterial gas tension. If the quite reasonable assumption be made that in health as well as in disease, the CO_2 of the arterial blood is in equilibrium with the CO_2 of the alveolar air, then the pressure of oxygen which should exist if a similar equilibrium existed with regard to O_2 can be calculated from the over-all R Q The difference between this "ideal" oxygen pressure and the O_2 tension actually found in the arterial blood is expressed as the "alveolar-arterial gradient" This gradient is increased in the presence of a defect of gas diffusion in the lung alveoli, but is also increased if much of the pulmonary blood is flowing through underventilated areas

Measurements of the Diffusing Capacity

Riley has further elaborated his technique of analysis of gas exchange by studying the function of the lungs using different concentrations of oxygen.

Using the shape of the oxyhaemoglobin dissociation curve, he is able to separate effects resulting from gas diffusion abnormality from those because of effective "shunts" of blood away from ventilated alveoli This striking contribution enabled the oxygen diffusing capacity to be calculated Unfortunately the method involves laborious gas analyses which demand a high degree of skill, and this approach is only possible in a highly organized and specially equipped laboratory

Attempts to obtain the same information by simpler methods have involved the use of carbon monoxide, the gas used by Marie Krogh in 1915 for the first determination of diffusing capacity. The fractional uptake of CO has been used in the assessment of pulmonary function (39), but the value of this measurement is much reduced by its sensitivity to the minute volume respired

In an outstanding contribution to this field, Filley (40) has used a method of calculating the alveolar pCO from the arterial pCO_2 The rate of uptake of CO is measured by a respiratory technique and from these figures the *"over-all diffusing capacity of CO" can be calculated Filley has found that* the diffusing capacity increases on moderate exertion. On more severe exertion there is no further increase in diffusing capacity A simplification of this method is to use a calculated value of the respiratory dead space, and thus avoid the necessity of measuring the arterial pCO_2 (41) Recent work showing the relative constancy of the respiratory dead space under different conditions (42, 43, 44) and for different gases (45) seems to justify this procedure, at least in adult subjects Further experience will be required to show whether the estimation of arterial pCO_2 is strictly necessary

Present techniques of measuring the diffusing capacity, whether with O_2 or CO, have demonstrated over-all diffusing capacity impairment in pulmonary infiltrations of various kinds (46), in cases of emphysema (47), and in some patients with mitral stenosis (48) There are indications that asthma is to be distinguished from emphysema principally by differences in diffusion in the well-ventilated parts of the lung (32) Considerable care must be exercised in the explanation of differences in this measurement in terms of pathological change Apart from the influence of kinetic factors, a fall in diffusing capacity might be attributable to loss of effective blood surface area, reduction in pulmonary capillary blood volume, or any factor causing physical interference with gas transfer such as alveolar thickening, or fluid between the capillary and the alveolar wall It is to be expected that further work will clarify these factors in a variety of clinical conditions

BRONCHOSPIROMETRY

Most of the tests described above could be applied to individual parts of the lung by bronchospirometry, and it seems reasonable to hope that they may prove of some value to the thoracic surgeon. Gaensler (49) has recently reviewed fully the technique of bronchospirometry from a considerable ex-

perience with the method, but it is not yet possible to form any opinion of the value of the investigation when applied to particular clinical problems It is to be expected that tests involving an analysis of gas diffusion will increase the value of the procedure.

THE VALUE OF FUNCTION TESTS

It will be realised that there are a considerable number of tests which are used to demonstrate impairment of function, and their value can only be established by making a large number of observations on normal individuals, *on patients with emphysema and other diseases, and* by showing either that they are sufficiently discriminating to be of diagnostic value or sufficiently accurate and consistent to be of prognostic value. It is important to realise that no single pulmonary function test can convey a full understanding of the defects of function in chronic lung disease. The status of pulmonary function tests is comparable to that of tests of function in chronic renal and hepatic disease Although no single test is diagnostic of hepatic cirrhosis, that disease produces a pattern of abnormal function that can be recognised by a suitable combination of tests In respiratory disorders similar "patterns of dysfunction" can be recognised. A suggestion has been made that a group of function tests might be combined together statistically to increase their diagnostic significance (50), but at the moment there is insufficient information to enable this to be done.

Diagnostic

Emphysema.—This disease produces a characteristic pattern of function impairment. In severe cases, there is an increased functional residual capacity with a reduced vital capacity and gross impairment of M.V.V. There is marked unevenness of gas distribution within the lungs and the over-all diffusing capacity is found to be much reduced. The clinical diagnosis of classical severe emphysema presents no difficulties In our experience diagnostic difficulty arises particularly in four different circumstances

(*a*) Patients who have minimal antecedent bronchitis. Certain patients are seen in whom there is a clear history of progressive exertional dyspnoea with minimal antecedent bronchitis We have encountered a small number of these patients in whom the onset of the disease has occurred in the third or early in the fourth decade of life In every case the demonstration of gross abnormality in ventilatory, mixing, and diffusion indices has been of considerable value in confirming the diagnosis

(*b*) A second group of cases are patients who are unreliable witnesses in regard to the principal symptom of exertional dyspnoea Emphysema, in common with any other organic disease, may be accompanied by a variety of symptoms of evidently psychogenic origin In such cases, objective evidence of abnormality furnished particularly by the finding of impaired gas mixing and diffusion, or with evidence of mechanical change, is of great

value. In these patients, objective tests of function not involving the patients' voluntary effort are of particular value.

(*c*) A third group of cases are the subjects in whom the presence of emphysema is suspected in addition to other known disease. We have found this differentiation particularly valuable in the presence of heart disease or hypertension. In a number of cases in whom a clinical diagnosis of emphysema seemed likely, the relative normality of the mixing efficiency and diffusing capacity have indicated that pulmonary congestion alone was present

(*d*) There is no doubt that many physicians regard the presence of a barrel-shaped chest as synonymous with pulmonary emphysema, and little doubt that this attitude has led to some of the discrepancies between clinical diagnosis and post-mortem confirmation of the presence of emphysema (51). In our experience the presence of a barrel-shaped chest, with absence of the area of cardiac dullness and faint breath sounds, cannot be taken of itself to indicate emphysema In such elderly patients, the residual capacity/total lung volume ratio may also be at the upper limit of normal, and well above the figure chosen by some authors to indicate the presence of emphysema (14, 52). These subjects have no bronchitis and no dyspnoea and further testing usually shows a normal index of intrapulmonary gas mixing and a normal diffusing capacity for a subject of equivalent age.

ASSESSMENT

Function tests have been used in a number of conditions in which the difficulty is not one of diagnosis, but of assessment of the severity of the abnormality. This aspect of pulmonary function investigation is of particular interest in asthma, chronic bronchitis, and pneumoconiosis, and recently developed methods of measurement have led to the use of respiratory tests in the assessment of patients with heart disease, and of patients who are candidates for major thoracic operations

Asthma—The disturbance of respiratory function in asthma, provided this is uncomplicated by emphysema, is mainly ventilatory In general there is a reduction of vital capacity and M V V., and the functional residual capacity is usually increased Almost invariably there is considerable unevenness of gas distribution in the lung These tests of gas mixing are likely to be sensitive indications of abnormality in this condition, and evidence has been produced of demonstrable functional abnormality in the absence of auscultatory evidence of bronchospasm (32, 33) The diffusing capacity, however, appears to be normal in asthma in contradistinction to emphysema, a finding that suggests that in asthma the well-ventilated parts of the lung possess a normal alveolar membrane and are well perfused.

It would seem necessary to retain a clear distinction between emphysema and asthma when methods of treatment or functional disturbance are being investigated. To refuse to subdivide these conditions beyond a general

classification of "hyperinflation" is very likely to confuse the issues involved. A recent example of this (53) was the assessment of the effect of pneumoperitoneum on "emphysema" in which, of the six cases studied, three were women below the age of 26; "irreversible" emphysema must be very rare in women of this age.

Recent techniques of measurement of the intra-oesophageal and intra-alveolar pressures have led to the direct calculation of bronchial resistance in asthma (54, 55, 56). Much work remains to be done on the asessment of asthma and of bronchodilator drugs by these methods

Chronic bronchitis.—Although there are many studies of pulmonary function in the most common complication of chronic bronchitis, namely emphysema, there are few studies on chronic bronchitis without emphysema The clinical distinction between chronic bronchitis and emphysema rests principally on the assessment of the severity and constancy of the exertional dyspnoea In our experience, care must be taken in making a diagnosis of emphysema when dyspnoea seems to be variable and closely linked to the presence of bronchospasm

It is often difficult to assess a patient of this type when first seen since the physical signs of emphysema are unreliable (57), and radiological assessment may also be misleading (58). These patients often improve considerably either spontaneously or with the assistance of bronchodilator drugs If any number of them were to be included in a series of apparent cases of "emphysema," it might be wrongly concluded that a specific line of treatment was beneficial in emphysema

If cases of chronic bronchitis with dyspnoea attributable to bronchospasm or bronchiolar obstruction are compared to cases of established emphysema, it will be found that the only two tests of function that discriminate between these groups are the M.V V to a small extent, and the diffusing capacity of O_2 or of CO to a rather greater extent. It is not yet known whether these changes are paralleled by a difference in the arterial oxygen or CO_2 tensions.

From a functional standpoint, the most distinctive feature of emphysema is the drop in over-all diffusing capacity that is almost invariably found. This impairment follows a period of progressive ventilatory disability

Pneumoconiosis and Fibrosis.—The status of pulmonary function tests in the assessment of pneumoconiosis is not yet clearly established. Some of the early work began with the assumption that the residual capacity/total lung volume ratio was diagnostic of emphysema and this makes precise analysis of the results difficult. There is also evidence that the degree of functional impairment as shown by some function tests is not closely related to the radiological classification (59) It is to be expected that the comprehensive study of pulmonary function in coal miners' pneumoconiosis, shortly to be published by the Medical Research Council, will throw some light on this difficult problem. Preliminary work on the mechanics of lung ventilation suggests that the dyspnoea of pneumoconiosis may well be more closely

correlated with physical changes within the lung than with radiological change or change in single ventilatory tests The difficult problem of the analysis of function in miscellaneous cases of pulmonary fibrosis has been most ably discussed by Wright & Filley (28). They point out that fibrosis may disturb normal pulmonary function by six different mechanisms, and that consequently the pattern of function disorder is often complex and usually variable from case to case.

Heart Disease—The importance of physical changes in the lungs in cases of mitral stenosis has been pointed out in an earlier section. A stage in these studies has not yet been reached for the tests to be used in the routine clinical evaluation of patients with heart disease, but the close relationships between the patients' symptoms of dyspnoea and the objective finding of increased lung rigidity suggests that they may be so used in the future.

ADDENDUM

Apart from recent papers already mentioned, there have been a number of contributions to respiratory physiology of clinical interest during the past 18 months These include an analysis of the M.V.V and vital capacity in children and adolescents (60), a description of an ingenious radiological technique for the measurement of pulmonary circulation time (61) so far used only in dogs, a description of a histological method of calculating the respiratory surface of the lung (62); and several further contributions on the pulmonary circulation that are reviewed by Denolin (63) Bartels & Rodewald (64) have contributed a careful comparison of the "a−a gradient" measured by different techniques and this paper should be read in conjunction with that of Filley (40) Bergan (65) has published a study on differential lung function in different body positions Bannister (66) has reported on his greater ability to maintain athletic performance on 66 per cent O_2 than 100 per cent O_2 Three contributions are concerned with methods for the determination of functional residual capacity One (67) points out the errors inherent in any single breath technique; in the second (68) five or six slow breaths are used for equilibration This technique gives good results on repeated testing of a normal subject, but one would expect it to be erroneous in many cases of lung disease The third paper advocates a radiological technique for the determination of total lung volume, and the authors (69) in their introduction state that methods commonly employed for determination of total lung capacity are either tedious or expensive, which has not been our experience Factors involved in the "breaking point of breath holding" have been studied by Fowler (70) who demonstrates that neurogenic reflex factors are likely to be involved Several authors have studied the effects on emphysema and asthma of bronchodilator agents (71), pneumoperitoneum (72), ACTH[2] (73), intermittent positive pressure breathing (74), or physical exercises (75) Some of these agents are valuable in the

relief of bronchospasm, but convincing evidence of their efficiency in established emphysema is lacking.

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CONTRAST METHODS IN DIAGNOSTIC ROENTGENOLOGY[1]

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The past year has brought forth few new discoveries in the field of diagnostic roentgenology. There has been, in general, a consolidation of earlier advances, *with emphasis placed on the finer details of roentgen interpretation* The newer techniques of roentgen examination have been improved and extended so that many of the experimental methods of previous years have now become standard procedures in most x-ray departments

Since the reviewer's own interests have, to a considerable degree, centered about the subject of roentgen diagnosis through the use of contrast media, and because this subject is intimately related to all phases of diagnostic roentgenology, it has been selected as the topic for this review.

General Remarks

Progress in the field of roentgen contrast visualization has followed on the heels of technical advances in x-ray equipment manufacture. Rapid sequence roentgenography is essential for angiocardiography and certain other circulatory examinations, and apparatus suitable for this purpose has been developed. Swedish equipment is now available which permits the exposure of roentgenograms at a rate of up to 10 per sec., simultaneously in each of two planes at right angles to each other [Schonander, Fredzell & Busch (1)] The reviewer has had the opportunity of personally examining some of the angiocardiographic films of Kjellberg, and of Wegelius & Lind (2), made with this rapid film-changing equipment The quality of the films surpassed by far those presently obtainable by motion picture methods (cinefluorography). The finer anatomic and pathologic details were vividly protrayed. In tetralogy of Fallot, for example, the pulmonary valve stenosis was beautifully demonstrated, and the ventricular septal defect and overriding aorta were clearly depicted Although the machinery is cumbersome and expensive, it is now being marketed in the United States Rigler & Watson (3) and Mouquin & Durand (4) have also developed rapid film-changing devices, but these operate at a slightly lower speed and in a single plane.

Progress in this field has also depended to some extent on improvements in the contrast media used Many serious and even fatal reactions to the present intravenous media have occurred and the search for less noxious agents continues Sodium acetrizoate (Urokon) is now almost universally accepted as the safest of the intravenous preparations, but is still not without hazard, as will be shown later

[1] The survey of literature pertaining to this review was completed in August, 1954.

The most important recent advances in this field have resulted from the discovery of two new contrast agents: (*a*) propyliodone (Dionosil), an English product, which may replace iodized oil in bronchography, and (*b*) iodipamide (Biligrafin, Cholografin), developed in Germany, which provides a method of intravenous cholangiography hitherto unavailable. These will be discussed under appropriate headings.

Central Nervous System

Cerebral angiography.—Present contrast media for cerebral angiography are unquestionably hazardous, persistent hemiplegia and even fatal accidents are not uncommon following their use [Rowbotham *et al.* (5)] Recently, sodium acetrizoate (Urokon) has been advocated for cerebral angiography Gass & Jacobson (6), using only 5 cc of the 30 per cent solution per injection, reported no death or permanent neurological sequelae among 200 carotid arteriograms. However, Seaman & Schwartz (7) encountered 5 6 per cent major reactions among 125 patients receiving this medium, and Lin and his co-workers (8) reported one serious but transient reaction among 100 cases In our own experience, entailing the use of two carotid injections of 12 cc. each, we have witnessed the development of permanent hemiplegia in 1 of 16 cases in whom this drug was used Although sodium acetrizoate appears safer for cerebral angiography than its predecessors, it must be classed as potentially dangerous. Ethyl diiodostearate (Angiopac) was used for cerebral angiography by Léger (9) in 1952, with promising results, but no follow up report has been forthcoming.[2] There is still great need for an innocuous contrast medium for cerebral angiography

Greater emphasis is being placed on the importance of the venographic phase of carotid angiography. This requires serial films at a rate of approximately one per second, and various types of plate-changers have been designed for this purpose. It is the reviewer's conviction that the single film arteriogram is inadequate for the study of cerebral space-consuming lesions, since tumors in the parietal and occipital lobes and deep-seated masses near the midline often fail to displace the arteries visible on the angiogram [Wood (10)] It is in just such cases that venography may be most helpful, since the venous drainage of the brain is in a posterior direction and more deeply and centrally situated than the divisions of the internal carotid arteries In the frontal view contralateral displacement of the internal cerebral vein may be the only angiographic clue to a space-consuming lesion In the lateral view alteration of the so-called venous angle, formed at the origin of the internal cerebral vein in the region of the Foramen of Monro, may be of material assistance in localizing a lesion [Johanson (11)] We have found the venographic phase, usually best seen about three seconds after completion of the carotid artery injection, an important aid in the interpretation of cerebral angiograms

[2] Dodge, Uihlein & Grindlay (99), using ethyl diiodostearate for cerebral angiography in experimental animals, found that dogs reacted very poorly to it, but cats seemed to tolerate it well

The hope that the vascular appearance of a brain tumor, as demonstrated by cerebral angiography, might permit an accurate prediction of its histologic nature has not materialized. As Wickbom (12) and others have noted, such tumors as glioblastoma multiforme, meningioma, and certain types of cerebral metastases often reveal abnormal vascular patterns which are fairly characteristic. However, it is also true that the same tumors may fail to reveal such abnormalities, and that similar tumor circulation may be seen in other neoplasms. Our experience would indicate that most cerebral tumors show no "typical" patterns. It is, therefore, seldom possible to predict with assurance the microscopic structure of a brain tumor from its angiographic appearance.

The procedure of visualization of the basilar artery and its branches by means of vertebral artery injection is gaining adherents despite the troublesome technical problems involved. Two approaches have been utilized: cut-down or percutaneous needling of the vertebral artery in the neck, and retrograde passage of an arterial catheter from the brachial artery into the subclavian to the point of origin of the vertebral [Radner (13)] In a limited experience with both methods we have encountered difficulty in obtaining adequate films and in interpreting them We have found the catheter method too time-consuming for practical purposes. We soon realized that minor displacement of the basilar artery and its branches could not be relied upon as a sign of an expanding lesion in the posterior fossa because of the normal variation in the course of these vessels from patient to patient and even from one side to the other in the same patient However, the Swedish neuroroentgenologists have shown that these difficulties are not insurmountable Olsson (14) has indicated the value of vertebral angiography in the diagnosis of acoustic nerve tumor, demonstrating not only displacement of the branches of the basilar artery but also abnormal circulation in the tumor itself. Olsson (15) and Sjögren (16) have collected a large series of cases and stressed advantages of vertebral arteriography in the detection of posterior fossa lesions Decker (17) found 26 cerebellar tumors among 150 vertebral angiograms and believed that the vascular displacement in such cases was so distinctive that the patients could be operated upon without ventriculography.

Venography of the skull and dural sinsues—Dural sinus venography by direct injection of contrast medium through a trephine opening into the sagittal sinus has proved of diagnostic value in sagittal sinus thrombosis. This procedure is probably indicated in all cases of so-called "pseudotumor" (increased intracranial pressure without tumor, obstruction, or other explanation) since sagittal sinus thrombosis is sometimes the cause of this condition

Fischgold *et al* (18) modified the technique of dural sinus venography by injecting the medium into the sagittal sinus in a counter-current direction. The communications between the facial veins and the intracranial venous system were thus demonstrated Using another variation in technique they successfully opacified the fine venous channels in the falx and tentorium, but this was associated with serious complications and the method was abandoned. Visualization of the diploic veins and their communications by direct

injection of contrast medium into the bone marrow of the calvarium was also accomplished by these authors.

Indications for the use of dural sinus venography seldom arise, but when they do we have found the information obtained to be well worth the small effort entailed in performing this procedure.

Pneumography.—Few important changes in the technique of pneumoencephalography and ventriculography have been advocated in recent years Shapiro & Robinson (19) and Falk (20) have re-emphasized the value of performing pneumoencephalography with small quantities of air, advocated earlier by Robertson (21) and Lindgren (22). The air is injected into the lumbar canal before the removal of spinal fluid so as to reduce the danger of herniation of the brain stem into the cervical spinal canal in patients with increased intracranial pressure. With the patient upright the head is positioned so that the air, rising from the lumbar canal, enters the fourth ventricle. This method results in a more frequent and vivid portrayal of the aqueduct of Sylvius and fourth ventricle, which are notoriously poorly visualized on pneumoencephalograms made by the conventional method of prior removal of spinal fluid and replacement with large quantities of air.

So far, our experience with controlled pneumoencephalography supports the contention that this technique is a distinct improvement over other methods and, in addition, is much less disturbing to the patient

Cardiorespiratory System

Angiocardiography—It is generally conceded that sodium acetrizoate (Urokon) is the safest contrast medium presently available for angiocardiography. Dotter, Wetchler & Steinberg (23) had no serious reaction or fatality among 450 angiocardiograms performed with this medium. It is, however, not entirely without danger, as attested to by the fact that our only death due to angiocardiography resulted from its use This fatality occurred among a group of 10 angiocardiograms performed with 50 cc of 70 per cent sodium acetrizoate The patient was an ambulatory non-cyanotic female, aged 29, who was later shown to have a large ventricular septal defect. Cardiac arrest developed immediately after the injection of the contrast medium, and the patient died despite thoracotomy and cardiac massage

Mention has already been made of equipment now available for "rapid fire" film-changing, with 6 to 10 exposures per sec in two planes simultaneously This permits two angiographic series (e g anteroposterior and lateral) with a single injection, thus lowering the risks of the method. The rapid exposure rate is of particular value in angiocardiography, as it reveals diagnostic details heretofore impossible to detect

Another improvement in angiocardiographic technique has been the injection of the contrast substance through a catheter advanced into the right heart. This method was advocated by Davies and his co-workers (24) in preference to the conventional method of needle puncture of the antecubital

vein, because the relatively smaller dilution of the contrast medium by blood enhances the degree of opacification of the cardiac chambers

The indications for angiocardiography in heart disease are becoming well-established. In congenital lesions in which the differential diagnosis is not clarified by clinical study or cardiac catheterization, angiocardiography may be of great help in establishing the diagnosis and in determining the feasibility of surgical correction This is particularly true in cyanotic cases, e g. tetralogy of Fallot, transposition of the great vessels, pulmonary stenosis with septal defect, and tricuspid atresia On the other hand, in such noncyanotic conditions as pure septal defects, angiocardiography often fails to visualize the shunt because it is directed from the left heart toward the right, thus opposing the flow of the contrast medium In these cases cardiac catheterization usually affords the desired information. In both coarctation of the aorta and patent ductus arteriosus angiocardiography often fails to visualize the lesion adequately because of the considerable dilution of the medium during its transit through the heart and lungs, before it reaches the site of the anomaly.

In acquired cardiovascular conditions angiocardiography has been particularly useful in distinguishing between cardiac enlargement and pericardial effusion. The thickness of the pericardial envelope about the heart can be estimated on the frontal angiogram from the distance between the right border of the cardiopericardial silhouette and the right border of the opacified lumen of the right atrium. Allowing a few millimeters for atrial wall thickness, the remainder is attributable to the pericardial sac and any fluid contained within it.

The selection of patients for mitral valvulotomy has been complicated by the difficulty in determining the presence of associated mitral insufficiency, a relative contraindication to surgery at the present time Clinical, radiological, and cardiac catheterization studies have as yet failed to resolve this problem Zinsser & Johnson (25) advocated angiocardiography for this purpose They found that in pure mitral stenosis there was a prolonged and dense opacification of the left atrium while in mitral insufficiency the left atrium and ventricle showed approximately the same radiopacity Utilizing their technique we have attempted this distinction by angiocardiography in six cases In the single instance in which we made the diagnosis of mitral insufficiency by this method, no significant regurgitation was found at operation However, further experience will be necessary before the method can be properly evaluated

Pulmonary angiography —The incidental demonstration of abnormalities in the pulmonary vasculature during angiocardiography has led to the exploration of the potentialities of pulmonary angiography The technique is essentially the same as that of angiocardiography, but the purpose is to utilize the vascular pattern of a pulmonary lesion as an aid in its differential diagnosis.

Schissel & Keil (26) and De Clercq and his co-workers (27) claim that this procedure has particular merit in the diagnosis of bronchogenic carcinoma, revealing diminished vascularity within and distal to the primary tumor mass. Steinberg & Dotter (28) confirmed these findings, but feel that unsupported angiographic evidence should not be considered conclusive, since nonneoplastic lesions may show similar changes. Schoenmackers & Vieten (29) performed post-mortem pulmonary angiograms in 86 cases of tuberculosis, silicosis, and bronchogenic carcinoma. They concluded that the similar appearance of the vascular tree in these three conditions precluded their differential diagnosis by angiography.

Our personal experience with pulmonary angiography is limited In several instances we have demonstrated extrinsic pressure defects on the superior vena cava which subsequently proved to be caused by metastatic lymph nodes. For the present, at least, we would be reluctant to subject a patient to surgery solely on the basis of the vascular pattern of a pulmonary lesion, or to withhold operation because of evidence of lymph node compression of the vena cava.

Steiner & Goodwin (30) have utilized pulmonary angiography to study active pulmonary hypertension in patients with mitral stenosis. They found that in cases of mitral stenosis with pulmonary hypertension the secondary, tertiary, and smaller branches of the pulmonary arteries, especially in the lower lobes, were of smaller caliber than in those without pulmonary hypertension. Their findings were verified by pulmonary artery pressure studies obtained during cardiac catheterization.

Thoracic aortography—Injection of contrast medium through a catheter inserted in retrograde fashion from a peripheral artery into the thoracic aorta provides the most consistent method available for adequate visualization of this structure The opaque medium is injected at the actual site of the lesion, thus avoiding dilution by the blood Jonsson, Brodén & Karnell (31) used this method routinely in individuals with coarctation of the aorta or patent ductus arteriosus to demonstrate the pathologic anatomy and, thereby, to guide the surgeon in planning the operative procedure

Our experience with this technique [Helmsworth, McGuire & Felson (32)] indicates that its greatest value lies in differentiating aneurysm of the aorta and great vessels from other mediastinal tumors While it is true that coarctation and patent ductus can be beautifully demonstrated by this means, we believe that the method is time-consuming and not without risk, and is best reserved for those cases in which a diagnosis cannot be established by simpler methods

As previously noted, vertebral angiography can be successfully performed by a modification of this technique, but most neurosurgeons prefer to inject the vertebral artery in the neck Similarly, abdominal arteriography can be performed by the catheter method, but percutaneous injection of the abdominal aorta is a simpler and safer approach

By passing the catheter tip into the proximal ascending aorta the coro-

nary arteries can be opacified rather consistently [Di Guglielmo & Guttadauro (33)]. Following experimental ligation of a coronary artery branch in dogs we have been able to demonstrate the actual site of coronary occlusion by this method [Helmsworth *et al.* (34)] However, we have had one fatality among the 10 patients in whom coronary filling was attempted. Coronary arteriography is a hazardous undertaking and we believe it should not be performed in man until a safer contrast medium is available.

Direct cardiac angiography —Direct injection of contrast medium into a cardiac chamber in humans was reported by Núñez and Ponsdomenech (35) in 1951 They performed 45 cardiac injections in 30 patients without fatal accident Cregg & Smith (36) recently injected the left ventricle in six patients One developed ventricular fibrillation but survived after thoracotomy and cardiac massage. The remainder showed no ill effects

Bronchography.—Iodized poppyseed oil (Lipiodol) has long been accepted as the best available contrast medium for bronchography However, the one serious objection to its use is its persistent visibility on chest roentgenograms made long after instillation, in many instances obscuring observations of the natural course of the pulmonary disease Chiefly for this reason, the search for a better contrast agent has led in the direction of rapidly absorbing radiopaque media In recent years various water-soluble media have been developed for this purpose These have consisted of iodopyracet (Diodrast) or related organic substances, in hypertonic aqueous solution made more viscid by the addition of a cellulose derivative Although these water-soluble media clear rapidly from the lung, they have introduced a new objectionable feature, that of bronchial irritation. They require more thorough and time-consuming anesthesia, and even then many unsatisfactory bronchograms result [Peck, Neerken & Salzman (37)].

Recently a new type of contrast medium for bronchography, propyliodone, was developed in England [Tomich, Basil & Davis (38)] It differs from other media in that it is a suspension rather than a solution or an iodized oil It is available in two forms, aqueous and oily. Don (39), Holden & Crone (40), and Cummins & Silver (41) have reported that it clears rapidly from the lungs, does not cause significant bronchial irritation, and results in bronchograms of excellent quality.

We have had the opportunity of performing bronchograms with oily propyliodone [3] A comparison was made between the first 30 bronchograms performed with this medium and an equal number of unselected iodized oil bronchograms The technical quality, patient reaction, and clearance time of the contrast medium from the lungs were carefully observed The technical quality of bronchial visualization was found to be approximately equal with the two media No untoward reaction which might be attributed to either contrast medium was encountered as an immediate or late complication. The most important advantage of propyliodone over the iodized oil

[3] Supplied through the courtesy of Picker X-ray Corporation, White Plains, New York.

was the rapidity with which it disappeared from the chest roentgenogram. The average amount of clearing of propyliodone in 24 hours was about 90 per cent, and the lungs became completely clear within 72 hours As is well known, the iodized oil often remained in the lungs for weeks or even months Pathological material was available in seven cases after propyliodone bronchography and no significant inflammatory reaction which could be related to the contrast medium was encountered.

In our experience oily propyliodone has all the essential attributes of both iodized oil and water-soluble media without having their disadvantages. We feel that this medium, or one similar to it, will ultimately replace those currently used for bronchography [Wisoff & Felson (42)].

Gastrointestinal System

Cholecystography.—Iodopanoic acid (Telepaque) has largely replaced iodoalphionic acid (Priodax) as an oral medium for visualization of the gall bladder. The early reports indicating denser gall bladder shadows and fewer side effects have been borne out by further experience [Bercovitz, Gillette & White (43)]. Clear visualization of the normal cystic and common ducts often occurs with iodopanoic acid However, when using ordinary dosage, abnormalities in these ducts are seldom revealed because in such cases the gall bladder is also usually diseased and does not concentrate the medium sufficiently for opacification of the biliary tract.

Another new medium for cholecystography, ethyl triiodoalphionic acid (Teridax) does not produce the dense gall bladder shadows seen with iodopanoic acid It is excreted entirely in the urine and, therefore, roentgenograms do not show the colonic residue of opaque material encountered with iodopanoic acid which occasionally interferes with gall bladder visualization [Shapiro (44); Weinberg (45)] Such interference occurs so seldom that this disadvantage of iodopanoic acid is counterbalanced by the roentgen evidence that the patient took the medication, as attested by the opaque medium in the colon. In the reviewer's opinion, iodopanoic acid is the best all around cholecystography medium

Cholangiography—Contrast visualization of the bile ducts has become a routine procedure during biliary surgery in a number of institutions. Surgical exploration of the common duct increases the incidence of postoperative complications, yet not infrequently it fails to reveal stones subsequently shown to be present Operative cholangiography, by outlining calculi and revealing the patency and caliber of the ducts, offers considerable help to the surgeon in deciding which cases require common duct exploration [Behrend & Greenspan (46), Mehn (47)] In our experience with the method we have found it of inestimable value Mistakes in interpretation are infrequent, and usually can be avoided by careful attention to details The films are not always satisfactory because the portable x-ray equipment requires a prolonged exposure time. However, breathing and movement can usually be controlled by the anesthetist Portable x-ray equipment with higher output

is now available for operating room use, and produces films of better quality

The need for a cholangiographic method which permits the diagnosis of biliary tract disease before operation has led to some interesting developments Keil, Hegstrom & Zoeckler (48) performed cholangiography by injecting contrast medium directly into the fundus of the gall bladder through a peritoneoscope. Biliary tract abnormalities were found in 12 of 55 cases. Banche & Muratori (49) used a similar technique Nurick, Patey & Whiteside (50), utilizing a percutaneous approach, needled the liver until a bile duct was entered, and then injected contrast medium One fatality occurred among seven cases.

Recently Twiss and his co-workers (51) opacified the common duct in 23 of 31 post-cholecystectomy patients by the oral administration of a double dose of iodopanoic acid. With this dosage the iodine content of the bile was raised to such a level that unconcentrated bile could be visualized as it traversed the common duct. They demonstrated dilatation of the common duct in 10 patients, 9 of whom were suffering from "post-cholecystectomy syndrome" We have had no personal experience with this technique of oral cholangiography as yet, but it seems very promising

What may prove to be the most important contribution in this field in recent years is the development of iodipamide. This drug was synthesized in Germany as a contrast medium for intravenous cholangiography Its high iodine content (64 3 per cent) permits the demonstration of the hepatic and common ducts without the need for concentration of the bile by the gall bladder

Early reports in the German literature indicate that common duct dilatation and calculi are readily demonstrated with this medium [Frommhold (52), Hornykiewytsch & Stender (53), Huber & Stossel (54), Puschel (55); Gaebel & Teschendorf (56)]. More recently, reports have appeared in American journals confirming its value [Berk *et al* (57), Orloff *et al* (58)]

We have had the opportunity of performing 23 intravenous cholangiograms with this new drug [Schiff, Young & Felson (59)][4] There were no serious reactions following the injection of 20 to 60 cc , and only four patients developed even minor symptoms In five of the 23 cases the biliary ducts were not visible (in two of these jaundice presumably interfered with secretion of the iodipamide) In the remaining 18 patients duct visualization was often faint, but it was almost always possible to recognize dilatation of the ducts when this was present

In 11 of the 23 patients there was a history of cholecystectomy, yet in 9 of these the common duct was visible. In each it appeared normal in caliber and the diagnosis of common duct obstruction could be excluded In the remaining 12 cases preliminary oral cholecystography was performed with iodopanoic acid (Telepaque), and revealed a normal gall bladder in two in-

[4] Supplied through the courtesy of E R Squibb and Sons, 745 Fifth Avenue, New York City

stances and non-visualization in 10 Intravenous cholangiography was then performed The two normal gall bladders and their ducts visualized well In the 10 cases with a non-functioning gall bladder intravenous iodipamide gave the following results non-filling in three; opacification of the ducts alone in three; and visualization of the ducts and gall bladder in four In the latter group the gall bladder shadows were not densely opacified, suggesting that the concentrating function of these gall bladders was impaired. Radiolucent gall stones, not seen on oral cholecystography, were visualized in one instance by the intravenous method.

In two of the patients intravenous cholangiography proved particularly valuable. One gave a history of recurrent right upper quadrant symptoms some years after cholecystectomy. Oral cholecystography showed no visualization of the biliary tract. Intravenous cholangiography revealed a small gall bladder shadow (regenerated cystic duct?) containing stones, and normal hepatic and common ducts The findings were confirmed at operation The second case showed mild jaundice, and a diagnosis of hepatitis was made on the basis of liver function studies. Oral cholecystography showed no filling of the biliary tract Intravenous cholangiography revealed a greatly dilated common duct and a faint gall bladder shadow. At operation a large common duct stone was removed and the patient's symptoms subsequently disappeared.

In our experience, intravenous cholangiography results in the demonstration of the biliary ducts in a high percentage of non-jaundiced patients Perhaps its greatest benefits are obtained in the symptomatic cholecystectomized patient. Theoretically, opacification of the ducts without filling of the gall bladder is indicative of cystic duct obstruction, but more evidence is required before this can be accepted as fact The method should definitely not be considered a substitute for oral cholecystography, since the latter is highly accurate in the diagnosis of gall bladder disease. For the present, iodipamide cholangiography should be reserved for those cases in which biliary tract abnormality is suspected but cannot be demonstrated by conventional means

We believe that intravenous cholangiography is a safe and extremely useful procedure Iodipamide is not, in our opinion, the entire answer to the problem, since the density of the shadows produced by it leaves something to be desired, especially with regard to the demonstration of stones and the visualization of the distal end of the common duct. However, its discovery marks the first step toward the development of an ideal medium for intravenous cholangiography

Hepatography, splenography, portal venography.—It has long been recognized that contrast visualization of the liver and spleen would be useful in the diagnosis of primary and metastatic malignant tumors and other diseases of these organs In fact, for many years the intravenous injection of colloidal thorium dioxide (Thorotrast) has been used successfully for this purpose.

Unfortunately, the prolonged radioactivity of thorium has proved dangerous, and the procedure has been largely discarded.

Recently a new intravenous substance for this purpose has been introduced. Ethyl diiodostearate (Angiopac), in colloidal suspension containing particles about two microns in diameter, gives excellent opacification of the spleen about 15 minutes after injection, and fair visualization of the liver four to six hours after injection, according to reports by Camerman (60), Baronchelli & Rossi (61), and Grossmann (62) The splenic opacification lasts about five hours. Occasional moderately severe reactions, usually associated with pulmonary edema, follow the intravenous injection of the suspension, possibly because of the small particles in the blood stream. Tagliaferro & Zaccoce (63) have recommended the intra-arterial administration of the drug

Rigler, Olfelt & Krumbach (64) have successfully opacified the liver and spleen by a modification of the technique of abdominal arteriography (see below) They injected relatively large quantities of sodium acetrizoate (Urokon) into the upper abdominal portion of the aorta, flooding the celiac axis with the opaque medium. Films obtained four to eight seconds after the injection revealed a fairly dense opacification of the liver and spleen In hepatic cirrhosis the liver density was found to be reduced, and in metastatic carcinoma radiolucent areas could be seen as filling defects within the opacified liver.

We were able to demonstrate metastases in the liver by this method in one instance, and have also diagnosed a hemangioma (88) and a hepatoma by filling the abnormal vessels in these tumors with contrast medium injected into the abdominal aorta Bierman *et al* (65) have had similar success with catheter aortography (see below), directing the tip of the catheter into the celiac axis.

Steinbach *et al.* (66) have injected contrast medium into the intrahepatic portal venous system in 10 patients following percutaneous needling of an intrahepatic branch of the portal vein Tori (67) has visualized the hepatic veins in man by injecting contrast medium through a catheter passed from an arm vein into the right auricle, and thence via the inferior vena cava into the hepatic veins Some time ago we attempted hepatic vein filling in dogs by a method similar to that of Tori Since each of the hepatic veins had to be catheterized separately, the procedure was found to be tedious and only partially successful Venography of the portal and hepatic venous systems by liver puncture or by catheterization is impractical and hazardous

In the surgical treatment of bleeding esophageal varices several types of venous anastomoses have been recommended. Spleno-renal and portocaval shunting procedures are the most widely used, and each has its proponents. Obviously, in thrombosis or cavernous transformation of the extrahepatic portion of the portal vein the portocaval anastomosis cannot be performed Similarly, thrombosis of the splenic vein would preclude the

spleno-renal shunt. Furthermore, should the obstruction responsible for the varicosities be proximal to the portal vein (e g. in the splenic vein), portocaval anastomosis will not lower the venous pressure In view of these facts, opacification of the portal venous system with contrast medium injected into a branch of the mesenteric or splenic vein during operation has been recommended to demonstrate the site and extent of venous obstruction This procedure may obviate tedious dissection, and help the surgeon decide which type of shunt is indicated. Portal venography is rather simply performed with the use of portable x-ray equipment [Hunt (68)].

However, the percutaneous injection of contrast medium into the substance of the spleen, first recommended by Abeatici & Campi (69), supplies essentially the same information before operation The opaque medium immediately enters the splenic vein and passes rapidly into the portal vein The sequelae of laceration of the spleen are minimized if the procedure is performed the morning of the operation This technique is gaining in popularity [Rousselot, Ruzicka & Doehner (70); Bahnson, Sloan, & Blalock (71); Hallenbeck & Bruwer (72)]

We have adopted the splenic approach (performed in the x-ray department) in preference to operative portography because of the better quality of the roentgenograms, the advantages of the rapid film-changer, and the opportunity it offers the surgeon to plan his procedure in advance and to make the incision on the appropriate side of the abdomen In a very small series of cases we have already encountered one instance of splenic hemorrhage, and others have also recorded this complication [Walker, Middlemiss & Nanson (73)]. We believe the procedure is hazardous unless followed immediately by operation.

Genitourinary System

Intravenous urography—The use of 70 per cent sodium acetrizoate for intravenous urography in place of the more dilute contrast media usually injected for this purpose has resulted in improved intravenous pyelograms, according to Bohne & Christeson (74) and Nesbitt & Nesbitt (75). In addition to clearer visualization of the excretory system, a generalized opacification of the kidney (nephrogram) is obtainable if films are made a few seconds after the rapid injection of the concentrated medium, and this may outline an avascular area, such as a renal cyst [Porporis *et al* (76)]. However, reactions are more frequent with the concentrated medium, and we have recently learned of two instances of sloughs in the antecubital fossa following extravasation of the medium [Rosenberg (77)] Accurate placement of effective compression devices over the lower ureters, thus preventing the passage of contrast-laden urine into the bladder, will rather consistently yield intravenous pyelograms of high quality even with the more dilute contrast media. In the opinion of the reviewer the intravenous injection of any of the concentrated urological media presents a small but definite added risk which should not be taken for routine intravenous pyelography.

Extraperitoneal pneumography.—The injection of gas into the extraperitoneal tissue to demonstrate the roentgenology of the posterior abdominal and pelvic viscera is called extraperitoneal pneumography. The gas (usually air) may be injected either directly into the perirenal soft tissues by percutaneous needle puncture through the posterior abdominal wall or, as first advocated by Rivas (78), by injection into the presacral space through the perineum, the gas dissecting upward in the retroperitoneal soft tissues. By using a larger quantity of gas, dissection may even extend into the mediastinum. The direct approach has fallen into disrepute because of a number of fatalities resulting from gas embolism The presacral route is considered safer because the site of injection is relatively avascular However, gas embolism has been reported following presacral injection [Russ, Glenn & Gianturco (79)]

Extraperitoneal insufflation is now being used rather frequently for outlining mass lesions in the region of the kidneys and suprarenals, and for the detection and study of other abnormalities in the retroperitoneal space [Cadman & Tinckler (80), Hamm & Harlin (81), Renfer (82)]. It has been successfully combined with body section roentgenography in the visualization of the pancreas and of the thoracic mediastinal structures.

In a limited experience with the presacral method we have made an incorrect diagnosis of adrenal tumor on two occasions From an earlier review of over 100 insufflations performed in our institution by direct perirenal injection, we believe the roentgenograms of the latter are easier to interpret. We encountered only one serious reaction among these cases From present indications it would appear that the presacral approach is the safer, and has the added advantage of bilateral visualization with a single injection Perhaps the errors mentioned above will be avoided as our experience accumulates

Vascular System

Venography—Various techniques for opacification of the peripheral veins and venae cavae have been utilized in the diagnosis and localization of venous obstruction The usual site of injection of contrast medium has been a vein below the suspected region of obstruction, although retrograde flow has been utilized to determine the status of the valves in the veins of a lower extremity. Recently, it has been found that injection directly into the bone marrow is a safe, simple, and effective method of performing venography Begg (83) has recommended the following technique 20 cc of one of the dilute aqueous contrast media is injected rapidly into the bone marrow, appropriately centered roentgenograms being obtained at the end of the injection As in the case of splenic injection, the medium immediately enters the venous channels draining the injection site For opacification of the iliac veins and inferior vena cava the injection is made into the greater trochanter. The tibial tuberosity is used for visualization of the veins of the thigh, and the lower tibia or fibula for the leg veins The procedure offers intriguing

possibilities for the visualization of the deep veins of the body, and will almost surely find a permanent place in contrast visualization of the venous system.

Translumbar arteriography.—Further experience with the direct injection of concentrated contrast medium into the aorta by percutaneous translumbar needle puncture continues to bear out the value of this procedure. It has been widely accepted as the method of choice in the diagnosis of renal tumor masses and of vascular disease of the aorta and its branches [Creevy, Krumbach & Price (84); Lindgren (85); Shapiro (86)].

In an experience with more than a thousand translumbar arteriograms [Smith *et al.* (87); Felson (88)] we have had only one fatality attributable to the method. This was apparently the result of direct intraspinal injection of the contrast medium by a surgeon performing his first aortic puncture.

Translumbar arteriography affords the urologist many opportunities to gain important information difficult or impossible to obtain by other means. In ureteropelvic obstruction the presence of an anomalous renal artery can usually be ascertained at operation. However, arteriography informs the surgeon, in advance, how much of the kidney is supplied by the anomalous vessel. He can then decide more readily whether the vessel should be divided or a pyeloplasty performed instead.

In horseshoe and other congenitally malposed or fused kidneys the arterial supply varies from a single vessel supplying both kidneys to multiple anomalous vessels. Since operation on these congenitally abnormal kidneys is often necessary, the advance information supplied by abdominal arteriography will obviate accidental severance of anomalous arteries, and also prevent the tragic consequences of ligation of the only artery to a horseshoe kidney. Arteriography can be decisive in the differential diagnosis between congenital absence of a kidney and contracted or hypoplastic kidney.

Arteriography is of particular value in those cases of ureteral obstruction in which retrograde and intravenous urography are unsuccessful in visualizing the excretory system. Since the amount of circulation in the kidney is an important reflection of its function and its ability to recover from pathological processes, the demonstration of adequate circulation in the obstructed nonfunctioning kidney indicates that the damage is not irreparable and that alleviation of the ureteral obstruction is feasible. Conversely, a kidney shown by arteriography to have poor circulation should probably not be left behind at the time of ureteral surgery.

The differentiation between hypernephroma and cyst of the kidney is perhaps the most important urological indication for arteriography. We have been able to make this differentiation consistently in more than a hundred cases by the use of this method. Hypernephroma is recognized by the abnormal tumor circulation within the neoplasm, while renal cyst is identified by the absence of arterial filling in the region of the mass or by separation of the renal artery branches.

Translumbar arteriography is also assuming great importance in the

diagnosis and management of intrinsic disease of the abdominal aorta and its branches, in the light of the recent advances in arterial surgery [Bahnson (89); Blakemore (90); Boyd (91); Julian *et al.* (92); Wylie (93), Oudot & Beaconsfield (94)]. That not all expansively pulsating abdominal masses are caused by aneurysm was demonstrated in two of our cases subsequently proved to have neoplasm. Arteriography was normal in both instances. Selection of the type of surgery (wiring, excision, grafting, etc) and advance planning of the operative procedure are facilitated if exact information concerning the location, origin, and length of an aneurysm is available. This information can be be obtained by translumbar arteriography. Similarly, in arteriovenous fistula arteriography may be of considerable assistance to the surgeon by delineating the vessels involved and the size and number of communications

Thrombotic occlusion of the distal aorta (Leriche syndrome) is not an uncommon condition, and surgery has given encouraging results in controlling this disease. Translumbar arteriography has frequently been used not only to establish the diagnosis, but also to help the surgeon select and plan the appropriate operative procedure [de Wolfe *et al* (95)] Arteriography has also proved useful in the diagnosis and treatment of iliac and femoral artery thrombosis.

Abdominal arteriography seldom provides information of value in the diagnosis of the Goldblatt kidney since hypertension is rarely caused by narrowing of the main renal artery Constricted intrarenal artery branches are too small to be depicted by present techniques

Peripheral arteriography—The demonstration of arterial disease in the lower extremities by the injection of contrast medium via the femoral artery has been helpful in the diagnosis and management of peripheral arterial disease The site of arterial occlusion, the amount and direction of the collateral flow, and the status of the arterial wall proximal and distal to the occlusion are readily demonstrated by this method [Astle & Wallace-Jones (96); Messent, Steiner, & Goodwin (97), Milanes *et al* (98)]. This knowledge enables the surgeon to select the cases in which operation is feasible Although the danger of arterial spasm exists, complications are rare and the value of the information obtained appears to justify its use.

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DISEASES OF THE BONES AND JOINTS[1]

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Cortisone and ACTH[2]

Any discussion of rheumatoid arthritis always brings up for consideration cortisone and its derivatives. After nearly six years of experience the drug is recognized as a substance with effective therapeutic activities as well as a potent agent for control of pain Despite all the dire promises formerly made, cortisone properly used does not ablate adrenal activity or produce complete diabetes If prescribed with reasonable caution psychoses, compression fractures, rounded facies, buffalo hump, hirsutism, and high blood pressure usually can be avoided. It has been shown that these drugs can be given uninterruptedly for long periods with reasonable safety

The original recommendation of starting with 300, 200 and 100 mg. of cortisone a day has been modified. Most physicians start now with 100 mg. a day, reducing the dose as improvement occurs until a maintenance level is reached. Since cortisone is not curative but must be continued for long periods the least effective dose is desirable It is thought by some to be better to begin with 50 mg a day, increasing in increments of 12.5 mg until therapeutic levels are reached. It is well to remember that recent or active tuberculosis, true psychosis, osteoporosis, and severe hypertension are actual contraindications to the use of cortisone Mild diabetes does not contraindicate its use

In a long-term study of rheumatoid arthritis management with cortisone, Copeman and co-workers (1) noted that 17 of 20 patients with severe prolonged and crippling arthritis were able to return to their occupations during cortisone therapy. These patients were treated from 16 to 36 months, 14 of them for two years or over, with adequate functional improvement The daily maintenance dose varied from 37.5 mg in two cases up to 100 mg. in three others In this series the drug had to be stopped in one case because of severe depression and hypertension Several patients developed gastric ulcer which healed on medical treatment with slight reduction in dosage of cortisone. Treatment with cortisone requires constant medical observation of blood pressure, weight, and urine for sugar, and the patients should be under constant medical surveillance In properly selected cases it makes possible an increased range of activities and a fuller enjoyment of life.

Hydrocortisone (17-hydroxycorticosterone) is similar to cortisone in chemical composition, differing from it only in having a hydroxyl radical where cortisone has a ketone group at the eleventh carbon position in the

[1] The survey of literature pertaining to this review was completed in June, 1954

[2] The following abbreviation is used in this chapter. ACTH (corticotropin)

steroid nucleus. The metabolic activities of the two steroids are qualitatively similar but quantitatively different, being from one and a half to two times as great in hydrocortisone by different tests. Hydrocortisone is manufactured and supplied as a pure alcohol, hereinafter called hydrocortisone, and as an ester, hydrocortisone acetate. These compounds differ in solubility, absorption, and systemic effect. Hydrocortisone, the more soluble, is readily absorbed by the gastrointestinal tract and is given by mouth The acetate is less readily soluble, is effective on local application, and is used for intra-articular injections.

Hydrocortisone is more effective gram per gram than is cortisone, only about two-thirds of the dose of hydrocortisone being necessary compared to cortisone. Usually the toxic complications seem to be lessened on the same therapeutic effect. Patients often can be switched from cortisone and disagreeable or hazardous symptoms avoided [Boland (2)].

Hydrocortisone acetate is an effective drug used intra-articularly. Its use in this manner requires such small doses that toxic effects are entirely avoided. It is used in patients with only one or two involved joints or with one or two intractable joints not relieved with adequate doses of cortisone Besides being effective in rheumatoid arthritis it is helpful in osteoarthritis, gouty arthritis, acute traumatic arthritis, bursitis, and other diseases Hollander, Brown & Jessar (3) have tabulated the results of 10,197 intra-articular injections into 17 different joints and cavities and listed the failures as an average of only 14 per cent They listed 11 conditions in which this treatment was used with successes varying from 89 per cent in rheumatoid arthritis and gout to 20 per cent in the shoulder-hand syndrome. The doses used varied from 37 5 mg. in the hip, 25 mg in the knee, ankle, shoulder and wrist, to 5 to 6 mg. in smaller joints

The prolonged treatment of ankylosing spondylitis with ACTH was reported by West & Newns (4). Six patients were treated for 18 months to two years All the patients had advanced severe disease and no longer received benefit from aspirin, phenylbutazone, and deep x-ray therapy. All were severely incapacitated and unable to work. Treatment was with ACTH,[2] Acthar Gel and H. P Acthar Gel from 5 to 50 units a day Two patients developed high blood pressure. Five of the six had gratifying relief, being able to increase their ranges of activity and continue at work The authors believe that in really severe cases, who receive little benefit from x-ray therapy, prolonged adrenal stimulation is justified but that it should not be raised to a higher level or maintained for a longer period than is absolutely necessary. They believe that ankylosing spondylitis is sufficiently different from rhematoid arthritis to justify separate therapeutic trials as between adrenal stimulation, hydrocortisone, and deep x-ray therapy. In none of the patients was there evidence that the disease progressed under therapy and, in one, severe osteoporosis was corrected.

The effect of adrenal stimulation by purified ACTH Gel on patients with rheumatoid arthritis and spondylitis was reported by West (5). He found

that different levels of effect were produced in different patients by the same dosage He feels that in ACTH therapy the important factor is not the dose given but the level to which the secretion of corticosteroids is raised Eosinophil counts and changes in electrolyte metabolism are a good indication of adrenal stimulation during the first few days. The best method of controlling this therapy is by assay of urinary 17-ketogenic steroids He used a new method described by Gibson & Norymberski (6).

Strenuous objection to the use of cortisone and ACTH in rheumatoid arthritis has been raised by Duthie (7) on personal grounds after considerable experience. Because these drugs are not curative, because the disease may progress under their use, because dreadful complications may occur with prolonged use of full dosage, and because badly crippled patients with disease of long duration may not be helped, he feels their use is not justified He allows their use, preferably ACTH, for rapidly progressing cases. He states unequivocally that

> It is my personal opinion that in the light of our present knowledge and experience, there is no indication for the treatment of rheumatoid arthritis by the continuous administration of ACTH or cortisone
>
> The use of short courses of either hormone, but preferably ACTH, may be justified in severe and progressive cases where conservative measures have failed to control the disease process and when severe crippledom is likely The local use of hydrocortisone in the treatment of single joints is likely to be accepted as a useful method of treatment, free from complications and giving worthwhile relief of symptoms in a significant number.

Copeman (8) in the next article takes violent exception from the above viewpoint and refutes Duthie's arguments effectively. He points out quite justly that while the disease may progress under therapy it often does so without therapy The indications for long term therapy include selected cases whose structural damage does not preclude restoration of function to a useful degree, cases in which conventional therapy has not been effective, and contraindications do not exist The dose must be regulated and the patient should have competent medical supervision Under these circumstances many patients work, enjoy life, and prosper reasonably well

It seems strange that there is still objection to ACTH and cortisone because the disease is not cured and medication must be continued The same is still true without objections to the use of insulin in diabetes and vitamin B_{12} in pernicious anemia. As a matter of fact, no practical method has ever been offered to eliminate the necessity of eating three meals a day If the drugs finally become ineffective the patients have had varying periods, so far up to four years, of relief of pain, increased range of activity, loss of fatigue, and a brightened outlook on life. Why do so many doctors frighten patients about the possibility in the future of hypertension, diabetes, pathological fractures, and a rounded face when they have painful, debilitating, and disabling diseases such as rheumatoid arthritis and spondylitis at the present time? ACTH and cortisone are powerful drugs, but they can be and

have been used successfully by many physicians with reasonable safety to many patients.

A comparison of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis conducted by the joint committee of the Medical Research Council and Nuffield Foundation on clinical trials of cortisone, ACTH and other therapeutic measures in chronic rheumatic diseases yielded surprising results (9). This investigation was planned specifically to compare the relative efficacy of cortisone and another drug, usually regarded as efficacious in relieving symptoms and in improving the patients functional capacity, and, secondly, to study the evolution of the rheumatoid process during prolonged therapy with these different agents. It was agreed that the patients chosen for this study were to be from 2 to 59 years of age, have had polyarthritis of rheumatoid type affecting at least four joints, with bilateral involvement of either hands or feet, ankles, or wrists, and have had the disease at the time of entry to the trial for not less than three months nor more than nine months The patients were treated in six different centers in England, Scotland, and Wales and were divided into two groups as equally as possible according to sex and age Patients were assigned at random and treated either with cortisone or aspirin. Treatment in each group was standardized for the first two weeks, cortisone being given in doses of 300 mg, 200 mg, and then 100 mg. daily for the first seven days followed by 50 mg for seven days and aspirin given 6 gm. daily for seven days, then 2 gm. daily for seven days. After the second week, treatment was individualized Treatment in both groups was stopped for a week at each observation period to assess the patient's condition without treatment and observe the progress of the disease.

Observations on this group of 61 patients made one week, eight weeks, thirteen weeks, and approximately one year after the start of treatment revealed that the two groups had run a closely parallel course in nearly all recorded characteristics; namely, joint tenderness, range of movement in the wrist, strength of grip, tests of dexterity of hand and foot, and clinical judgements of the activity of the disease and of the patients functional capacity The hemoglobin and blood sedimentation rate were slightly more favorable in the group treated with cortisone

The physiological disposition and fate of hydrocortisone and cortisone in man and animal was discussed by Peterson *et al* (10). The biological half-life or the time required for 50 per cent of intravenously administered non-radioactive steroid (200 mg crystalline free or alcohol hydrocortisone, or cortisone in 500 cc 5 per cent dextrose over a 30 min period) to disappear from the plasma is shown in Table I.

Measurement of the excretion of infused tracer quantities (700 μg.) of radioactive C^{14} hydrocortisone in normal subjects revealed that more than 80 per cent of the dose is excreted in the urine in the first day, an additional 4 per cent during the next 4 days and the remainder is excreted in the feces. Of the corticosteroids present in the urine, only 4 per cent of the radioactivity

TABLE I

THE TIME REQUIRED FOR DISAPPEARANCE FROM THE PLASMA OF 50 PER CENT OF INTRAVENOUSLY ADMINISTERED STEROID

	CORTISONE			HYDROCORTISONE		
	Mean (minutes)	Range (minutes)	No. of Patients	Mean (minutes)	Range (minutes)	No of Patients
Normal subjects	62	54–92	7	118	104–130	12
Rheumatoid Arthritis	54	35–82	5	111	67–164	5
Liver Disease	82	52–112	6	358	160–800	8
Hyperthyroid	32	—	1	55	—	1

was recovered as "free" steroid, 13 to 25 per cent was conjugated as glucuronide, and an additional 15 to 25 per cent was hydrolyzed with boiling hydrochloric acid The quantity of radioactive steroid extracted from the urine with organic solvent both before and after hydrolysis was only 40 to 60 per cent of the total urinary radioactivity.

Studies on the metabolism of adrenal cortical steroids in the synovial cavity in rheumatoid arthritis by McEwen, Wilson & Ziff (11) showed that cortisone and hydrocortisone, both free alcohol and acetate, disappear rapidly after intra-articular injection One-half hour after injection of 100 mg of hydrocortisone (free alcohol) 78 per cent had disappeared. One hour after injection of 50 mg. of both hydrocortisone and cortisone acetate 86 per cent had disappeared and three hours after injection of 100 mg. of both drugs (free alcohol) 97 per cent had disappeared Evidence indicates that metabolites are found in the joint The authors believe that the locally-acting anti-inflammatory agent may be one of these metabolites rather than compound F itself, or that a metabolite may share this activity with compound F.

The local anti-rheumatic effectiveness of higher esters and analogues of hydrocortisone was studied by Hollander *et al* (12) Previous investigations of the disappearance of hydrocortisone from the synovial fluid revealed the absorption of the injected hormone by the cells of the synovial fluid and particularly by the lining cells of the synovial membranes The most significant finding was that hydrocortisone acetate was absorbed and retained by the lining of the synovium without splitting the ester whereas unabsorbed hormone in the joint fluid was rapidly hydrolyzed and broken down. They assumed that higher and less soluble esters of hydrocortisone would likewise be absorbed unchanged by the synovial membrane and might have a longer anti-inflammatory effect Five such compounds were compared with hydrocortisone acetate, and the results were tabulated according to the duration of relief. Allo-dihydro-F was distinctly inferior, 9-alpha-chloro-F, F-caprylate, and F-benzoate were about equal, and F-butyl acetate was effective

twice as long as compound F. F-butyl acetate was superior to compound F in degree of improvement in 65 per cent of cases and in duration of improvement in 59 per cent.

Bayles, Boland & Bunim (13) each independently discussed 9-alpha-fluorohydrocortisone It was described as several times to as much as 10 times as potent as hydrocortisone (free alcohol). It was definitely stated, however, that this drug had salt retaining properties; also, it produced marked elevations in blood pressure. It would seem that this drug will be of little therapeutic importance and is of interest only from an academic point of view.

Phenylbutazone

Phenylbutazone (Butazolidin) continues to arouse much controversy At its introduction to the *American Rheumatism* Association Meeting in New York, April 20, 1954, men climbed the rostrum in droves to extoll its virtues At the next meeting they seemed unable to say enough against it. The consensus today is that this is a powerful and effective drug with great potentialities of harm In a general discussion of the matter Hart (14) points out that it has marked analgesic effects without being at all anti-inflammatory or having any influence on adrenal action It relieves the symptoms of fibrositis, osteoarthritis, gout, rheumatoid arthritis, periarthritis, ankylosing spondylitis, and other painful conditions of bones, ligaments, and joints

In rheumatoid arthritis a high proportion of patients are relieved of symptoms without showing evidence of objective improvement Pain and stiffness are often reduced but swelling is slightly if at all affected The relief in gout is prompt and dramatic. Osteoarthritis and ankylosing spondylitis are also effectively relieved Phenylbutazone causes a retention of sodium chloride and water so that edema may follow its use

Complications occur in a high proportion of cases and necessitate the discontinuance of the drug They have been reported in 20 to 40 per cent of cases in different series They vary in severity from agranulocytosis with death, exacerbation of peptic ulcers, thrombocytopenic purpura with bleeding, to nausea and vomiting Since smaller doses have been used (200 to 400 mg instead of 800 to 1200 mg per day), toxicity has been reduced Hart recommended limiting the dose to 200 mg once or twice daily and withholding the drug every fifth or seventh day

Currie, Peebles Brown & Will (15) treated 429 cases of rheumatoid arthritis with phenylbutazone, some of them for as long as one year with notably few complications Twenty showed side effects but only three had to stop treatment The authors conclude that this agent affords rapid and substantial relief in a large proportion of patients with rheumatoid arthritis, with an apparent suppression of disease activity in many cases Almost all cases relapse slowly on withdrawal of the drug They consider the drug remarkably free from serious toxic properties

The relation between the toxic and therapeutic effects and the blood

levels during phenylbutazone therapy was reported by Bruck *et al.* (16). They studied 48 patients with rheumatoid arthritis as outpatients and four patients were hospitalized for detailed short-term studies of blood, bowel, and urinary excretion. All patients received phenylbutazone by mouth on different dosages for a month. The average blood levels attained varied from 5.5 mg per 100 ml. on 200 mg. per day, 7 8 mg per 100 ml on 400 mg. per day, 9.5 mg. per 100 ml. on 600 mg per day, and 12.8 mg per 100 ml. on 1200 mg per day. The incidence of toxic symptoms as well as the degree of improvement varied directly with the blood level Among the patients 48 per cent noted toxic effects These included, in decreasing order of frequency: epigastric pain and vomiting, dry mouth, buccal ulceration, edema, urticaria, diarrhea, headache, purpura, and renal failure

A report on the long-time effect of phenylbutazone in rheumatoid arthritis was given by Steinbrocker *et al* (17) at the New York Rheumatism Association Meeting Sixty-nine per cent of 48 patients observed for as long as two years had appreciable benefit One-half of them were still receiving the drug at an average dose of 300 mg per day Seven of them had it for six months to a year, 17 had it for over a year. Grade 2 response (American Rheumatism Association system of rating) has been maintained Nine patients stopped because they no longer needed it, suggesting that they were in temporary remissions Nine patients were stopped because they noted no benefit After six months of good tolerance, six patients were discontinued because of severe toxicity Intolerance seemed to occur as frequently after prolonged administration with the same frequency as it did in short time trials Two had vomiting and diarrhea; two had melena and hematemesis, two patients had gastrointestinal hemorrhage six months after treatment was stopped, one patient developed hypertension and another anemia, with symptoms disappearing after the drug was stopped

Fifty cases of rheumatoid spondylitis were treated with phenylbutazone for 2 to 12 months by Toone & Irby (18), of these 27 showed major improvement, 8 showed minor improvement, and 15 were considered failures Toxic reactions occurred in 17, in 3 of whom the drug had to be discontinued The average dosage schedule was 600 mg for three days followed by a maintenance dose of 100 to 400 mg A favorable response, if maintained for two months, will usually continue In nine cases phenylbutazone was considered the treatment of choice.

The comparative effects of ACTH and phenylbutazone in rheumatoid arthritis were reported by Mason (19) Both drugs were used consecutively in six patients He found that they differed in their effects ACTH produced a fall in erythrocyte sedimentation rate, a rise in 17-ketosteroid and glucocorticoid excretion, and a diminution in the joint swelling Phenylbutazone was not shown to have had any effect on erythrocyte sedimentation rate, did not alter consistently 17-ketosteroid and glucocorticoid excretion, and had no effect on joint swelling Both drugs seemed to have roughly the same effect on subjective symptoms as well as on function tests

Kidd, Boyce & Freyberg (20) conducted studies on Butapyrin (a mixture of phenylbutazone and aminopyrine) and phenylbutazone in rheumatoid arthritis, rheumatoid spondylitis, and gout. Since the therapeutic effects were equal but toxic symptoms occurred much more frequently with Butapyrin (68 per cent compared to 26.7 per cent with phenylbutazone), the first drug was discontinued. The effects in rheumatoid arthritis were equal to those described elsewhere. The effect in gout was dramatic, however, because it produced rapid and excellent clinical improvement in a high percentage of patients with acute gouty arthritis. It also reduced plasma uric acid levels, apparently without increasing uric acid excretion. This the authors believe to be a unique effect worthy of further study in an attempt to recognize the fundamental metabolic defect in this disease.

Death from phenylbutazone has been ascribed to agranulocytosis One death due to hypersensitivity has been described by O'Brien & Storey (21) It occurred in a 73-year-old man with rheumatoid arthritis who took phenylbutazone 200 mg. twice daily for five weeks. His face then began to swell, his eyes watered, and his mouth became very dry and sore He drank more fluids and noted his urine was scanty and reddish brown. He became short of breath, drowsy, and complained of tingling He died suddenly four days after entering the hospital Autopsy showed polyarteritis nodosa, hypersensitivity, angiitis, and granulomatous lesions throughout many organs and tissue

Gout

An excellent review of the modern concepts of gout has recently been presented by Gutman (22) Primary gout is shown to be a constitutional hereditary disease associated with abnormalities of uric acid metabolism About one-fourth of the relatives of gouty patients have abnormally high levels of blood or serum uric acid This is attributable in part to increased production of endogenous uric acid Two gouty subjects were shown to produce uric acid at three times the normal rate by means of labelled N^{15} glycine Secondary gout depends upon high uric acid production in connection with diseases such as polycythemia and the leukemias

The metabolism of purines and uric acid production is clearly explained and the role of the kidney is discussed It is strange that 90 per cent of urate filtered through the glomeruli should be resorbed by the tubules, a rate of resorption comparable to that of essential electrolytes and metabolites Interference with tubular resorption is a fundamental principle of successful therapy

Three effective agents are available for control of acute gouty attacks. colchicine, ACTH, and phenylbutazone Colchicine is given orally in doses of 0.5 to 1 0 mg every 2 to 4 hr until the attack subsides or diarrhea, nausea, or vomiting occurs A substantial proportion of gouty patients cannot tolerate therapeutic doses of colchicine ACTH is effective in most acute gouty attacks Doses of 50 to 200 mg are injected initially and daily doses

of 50 to 100 mg continued for several days Thereafter doses are tapered off and small doses of colchicine (1 to 2 mg. a day) are started. If ACTH is stopped too suddenly, another attack is liable to occur. Phenylbutazone in daily oral doses of 0.6 to 0 8 gm usually gives rapid relief. Toxic effects occur but are usually not serious for the short times needed in gout.

Gouty attacks seem to be inhibited by low purine diet. Chronic tophaceous gout is prevented or relieved by probenecid (Benemid).

The effects of uricosuric drugs on uric acid excretion were discussed by Gutman *et al.* (23). Probenecid in 1 0 gm daily oral dose increases urinary urate output by 50 per cent with corresponding falls in serum urate levels. Phenylbutazone has a uricosuric effect only on blood levels over 10 mg per cent After intravenous injection (12 to 27 mg/K) the ratio of the clearance of water to that of inulin rose within 2 hr to a 3-fold peak and uricosuria lasted 24 hr. Renal effects of salicylate are complex. Plasma salicylate levels of less than 5 mg per cent lower urate excretion· levels above 12 mg per cent cause a 3½-fold rise of urate excretion of short duration. In oral dosages best tolerated clinically, probenecid is the most potent and selective uricosuric agent examined.

Studies on the effect of probenecid on gout reported by Mason (24) showed an effective lowering of blood urate level and an excretion of urate so great as to defy explanation The calculated loss of uric acid from plasma, estimating the latter as 5 per cent of body weight, averaged 149 mg in five days The excess appearing in the urine was 2,136 mg It seems likely that the excess was absorbed from tophi since these discrepancies became less marked on larger experiments, when equilibrium was reached Five of seven patients had acute attacks of gout occurring after blood levels had been reduced, at times to normal

Rheumatoid Arthritis

Certain unusual clinical details of rheumatoid arthritis have been reported Fistulous rheumatism (25) occurs about joints which are the sites of severe bone destruction and bone absorption, resulting in the extrusion of bone fragments There is often thick yellow pus due to infection with *Staphylococcus pyogenes*

Finger contractions (26), though very common in advanced cases of rheumatoid arthritis, were seen in three cases as the only evidence of the disease. The tendons showed typical changes of rheumatoid arthritis Two of the three cases were greatly helped by conservative treatment and two others were improved by operation

Heel lesions associated with sub-Achilles bursitis which eroded the os calcis and finally obliterated the bursa, and erosion of the plantar surface of the os calcis by fibrinoid-containing tissue, closely resembling a rheumatoid nodule, were described as occurring in 19 cases by Bywaters (27)

A striking case of rheumatoid arthritis is described by Jacqueline (28) This woman who suffered a right-sided hemiplegia of uncertain origin and

who never had proper use of her right arm or leg was seen at 52 to have well-marked advanced rheumatoid arthritis with flexion deformity and enlargement of the metacarpo-phalangeal joints and marked ulnar deviation of all the fingers. The radiograph shows destruction of the distal ends of the metacarpal bones Photographs and radiograph of the right hand are completely normal The occurrence of Heberden's nodes on the sound side, the hemiplegic side being spared, had been previously reported.

Osteoarthritis

Perhaps it is fair to say that something new has been added to our knowledge of osteoarthritis. Harrison, Schajowicz & Trueta (29) have studied the nature and evolution of the disease in the hip Their investigation is based on 91 post-mortem examinations of the hip, 45 femoral heads removed at operation, and radiographs of 80 selected patients suffering from osteoarthritis of the hip and who were followed for several years. This material was studied by dissection and macroscopic examination, radiography, histology, and investigation of the vascular pattern of the osteoarthritic femoral head

The plan of the acetabulum indicates at once that the joint cartilage of the head of the femur is divided into two parts, one of which is weight-bearing, called the pressure area, and the other nonweight-bearing or nonpressure area Differentiation between pressure and nonpressure areas is shown by the main trabecular systems of the cancellous bone of the head A band of trabeculae running through the lower part of the femoral neck from the corticalis below to the articular surface takes the shape of a column, the upper part of which spreads out like a fan to support the pressure area Before maturity the band is lost at the epiphyseal line because trabeculation of the epiphysis is diffuse and unorganized

The beginning of the osteoarthritic process takes place in the articular cartilage. This is followed by osteophyte formation, flattening of the femoral head, eburnation, necrosis, sclerosis, cyst formation, and extrusion of the head The early changes in the cartilage usually start in the nonpressure area. Wear and tear has always been cited as the main cause of osteoarthritis The findings of these workers indicate that lack of pressure is more deleterious than pressure The term "aging" is applied to these cartilage changes, but they occur in the second decade and are not invariably more extensive at great age. The necessity for use and compression of cartilage to maintain cartilage health has been stressed The authors have described a series of vessels immediately beneath the cartilage Pumping action on these vessels aids cartilage nutrition

Cartilage degeneration is indicated by calcification Calcified areas are invaded by blood vessels and bone marrow Osteophytes are any new bone with marrow formed from calcified cartilage They are not restricted to new bone growing only at the periphery If the blood vessels of the osteophytes arise from synovial tissues they are called extracapsular vascularization

Osteophytes originating in medial nonpressure areas arise from vessels penetrating from the subchondral area or intracapsular vascularization. Osteophytes are always limited to nonweight-bearing areas. They are attempts to revitalize degenerating cartilage, a degeneration most commonly attributable to malnutrition caused by lack of alternating pressure. They occur most commonly about the corona of the head, about the fovea, and spread about the medial and lower surfaces of the head Osteophytes containing red bone marrow may cover original cartilage, accounting for the mass of bone often seen on the lower aspect of the head.

In the pressure areas the cartilage wears thinner and thinner, the trabeculae beneath become fractured and necrotic, the joint space is decreased or disappears, the head is flattened, and the joint surfaces become condensed and more than normally radiopaque. Cysts of varying size and usually multiple are invariably found in osteoarthritis. They are limited to pressure areas. If studied adequately, they are found always to open into the joint surface They are filled with connective tissue and fibrinoid cartilage and are surrounded by necrotic bone They seem to be attributable to infarction resulting from pressure and collapse The head of the osteoarthritic femur is shown to have an excessively rich blood supply and to be hyperemic It is thought that the pain of this disease is due to hyperemia, demineralization, weakening, and fracture of the trabeculations.

While in the course of this study, the authors felt the need for more exact information about the circulation of the head of the normal femur. In a study published earlier by Trueta & Harrison (30), they found that the blood supply to the epiphysis enters the head superiorly and posterosuperiorly through two to six lateral epiphyseal arteries which are spiral in form for a short distance after entry. The medial epiphyseal arteries enter the head through the fovea via the ligamentum teres and anastomose with the lateral epiphyseal arteries. The main flow of the epiphyseal arteries is into the epiphysis and toward the joint surface The outflow to the metaphysis is small. Superior metaphyseal arteries branch from the same stem as superior epiphyseal arteries, enter the superior aspect of the neck some distance from the margin of the articular cartilage, and have a straight course down into the bone About a quarter of the way across they turn superomedially toward the site previously occupied by the epiphyseal plate. The inferior metaphyseal arteries enter the bone close to the edge of the cartilage and distribute their branches through the metaphysis There is free anastomosis inside both the epiphysis and the metaphysis as well as between the two areas They noted no evidence of a nutrient artery from the femur. There is no appreciable diminution in blood supply of the head of the femur as age advances.

The marrow of the epiphysis is fatty marrow and the blood supply is by conventional capillaries. In the metaphysis the bone marrow is red and there are numerous sinusoids here instead of capillaries They emphasize the occurrence of a rich blood supply to the cartilage by capillaries piercing the

subchondral plate. This indicates that cartilage probably is more dependent upon blood supply and has a more active metabolism than has been suspected heretofore.

Another new and interesting concept of osteoarthritis has been presented concerning Heberden's nodes. The conclusions seem to have been arrived at independently by workers in Finland and in Italy. Peltola (31) in Helsinki and Roversi & Mars (32) in Milan both report the finding of exostosis in the cervical vertebrae so placed as to press upon branches of the cervical plexus Such abnormalities are very common in people with Heberden's nodes and their distribution corresponds to the distribution of finger involvement. They have not been found in a control series without Heberden's nodes The present reviewer has found similar conditions in the few cases he has checked. The findings are surprising because an intense and prolonged familiarity with Heberden's nodes has not heretofore revealed any evidence of circulatory, sensory, motor, or trophic disturbances in the fingers before or during the development of these exostoses. It is interesting to note that Heberden's nodes have failed to result in hands in which there is interference with the nerve supply, be this attributable to upper motor neuron lesion as in a stroke, to lower motor neuron lesion as in anterior poliomyelitis, or to peripheral nerve lesion after severance of the nerve. In the instances cited Heberden's nodes were seen in the other hand with normal nerve supply

The Robert Jones lecture of 1952 given by George Perkins and entitled "Rest and Movement" (33) is enough to gladden the heart and warm the soul of any rheumatologist. He demonstrates quite clearly that prolonged rest is the enemy of joint movement and that splinting may be necessary for short periods of inflammation, but that it is not necessary nor desirable when muscle spasm will hold bones in alignment. He cites a man with a fracture of the mid portion of the femur treated with plating and cast. After 10 months rest in the cast and shortly after starting to walk the plate broke and the fracture was found to be ununited He then started walking in a plastic cylinder. Union occurred 10 weeks later, and treatment was stopped. The point to be emphasized is that the patient never regained more than 15 degrees of motion of his formerly normal knee thereafter It has seemed to the author that much good orthopedic surgery in patients with rheumatoid arthritis is wasted by unnecessary and prolonged immobilization of joints resulting in adhesions, demineralization of bone, and muscle atrophy with resultant prolonged or permanent disability.

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LABORATORY AIDS TO DIAGNOSIS AND THERAPY[1]

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Methodology of Clinical Chemistry

Clinical Chemistry is a branch of analytical chemistry devoted to the application of analytical techniques to biological systems on the molecular level as aids to diagnosis, prognosis, and treatment Its operations may be divided into three parts. (*a*) isolation of the substance sought from interfering materials, (*b*) *reaction of the substance with a suitable reagent, and* (*c*) measurement of a product of the reaction. In a few instances when no appreciable interferences are encountered (enzymatic determination of urea, determination of bilirubin) or when the substance can be measured directly (photometric determination of hemoglobin, falling drop technique for serum protein) either one of the first two steps may not be required.

Frequently, the most time-consuming operation in an analytical method consists *in the isolation of the compound to be analyzed. This is particularly* evident in the procedure commonly employed in the hydrolysis and extraction of urinary keto-steroids and estrogens, in wet ashing and extraction of biological materials for heavy metal analysis, and in extraction, enzymatic dephosphorylation, chromatographic adsorption, and elution, required for the determination of thiamine The inconvenience of such procedures, rather than disinterest in the results, hampers the more frequent analysis of the substances in question As an outstanding illustration, sodium and potassium determinations have but recently become a routine procedure after the development of the flame photometer as a practical laboratory instrument

Preliminary isolation is necessary only when interfering substances are expected to be present. Although values obtained with Volhard's chloride method will also include bromide and iodide, only traces of these ions occur normally in biological fluids and may, thus, be ignored Again, since no interferences are encountered in the diazotization reaction for serum bilirubin, this procedure is performed directly without prior preparation of the sample The necessary degree of preliminary isolation of the ingredient to be measured depends upon the specificity of the reagent employed in the second step of the analysis. Thus, since urease acts specifically on urea, this compound may be determined in blood directly However, because ammonia is the product of urease activity which is usually measured, urea in ammonia-containing fluids must be determined after preliminary removal of ammonia or by correction for its quantity as found by separate analysis.

[1] The survey of literature pertaining to this review was completed in August, 1954.

Apart from considerations of convenience, simplicity, and sensitivity, a satisfactory knowledge of reaction mechanism and a stoichiometric yield of a measurable product are desirable and reassuring. Examples for well understood stoichiometric reactions are the titration of chloride ion with silver nitrate or of oxalate ion with permanganate. More frequently, one or both criteria are not attained. Nevertheless, under properly controlled conditions, equally useful and valid data may be obtained. Reducing reactions for sugar are not usually stoichiometric, just the same, reliable values may be derived by comparison with known concentrations of sugar. The Liebermann-Burchard color reaction for cholesterol is better known by name than by mechanism, yet its usefulness for the determination of cholesterol is not impaired merely because practical application has preceded our ability to interpret its mechanism.

The final measuring step generally requires specialized instrumentation Amongst these techniques, spectrophotometry, particularly in the visible range, has become the most widely used by virtue of the convenience, speed, and accuracy with which low concentrations of substance, commonly occurring in biological fluids, may be measured. Constituents of blood and urine, minor in concentration, but not necessarily in importance, are often amenable to photometric analysis by application of sufficiently sensitive color reactions Titrimetric procedures are usually employed when greater accuracy is required or when a measurable chromogenic system is not conveniently available. Gravimetric methods of analysis, employed in the early years of clinical chemistry, usually requiring excessive quantities of test material, have been mostly abandoned The gravimetric method for total serum lipids in petroleum ether extracts is still widely used, but a color reaction for lipids has been recently introduced [Swahn (89)] The systems of gasometry and manometry, developed by Van Slyke and his school, have enriched clinical chemistry with a wide variety of exact techniques The most convenient of these for routine clinical studies include methods for the determination of content and capacity of carbon dioxide and oxygen The recently introduced Kopp-Natelson micromodification of the Van Slyke manometric apparatus requires only 0.03 ml of the sample.

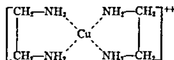
In the sections to follow some newer analytical developments of clinical interest will be presented.

Inorganic Serum Constituents

Chelating agents—Biochemical literature is replete with early applications of the principle of chelation in an essentially empirical way Gerhardt's test for acetoacetic acid with ferric chloride, the isolation of amino acids as heavy metal complexes, the biuret reaction of proteins with an alkaline copper reagent, and Fehling's solution for the detection of reducing carbohydrates, are a few examples for the early application of chelates and chelation reactions. The requirement for certain metal ions in some enzyme systems is

attributable to their ability to bind both enzyme and substrate into a chelated structure [Martel & Calvin (58)]. In recent years, increasing application of chelating reactions, paralleling the elucidation of the essential mechanism involved, has considerably simplified certain procedures, particularly the examination of metals present in low or trace concentrations.

A chelate is a complex between a metal ion and an organic compound, but differs from simple complexes, such as $[Ag(NH_3)]^+$, $[HgI_4]^-$, $[Fe(CN)_6]^{3-}$, etc. in that the non-metallic ligand is polyfunctional, i e. it contains two or more groups which react with the metal ion. The resulting structure, containing one or more rings, is usually more stable than related linear complexes Ethylene-diamine copper,



a bicyclic analog of $[Cu(NH_3)_4]^{++}$, is an example of a relatively stable chelate Five-membered and six-membered rings are the most stable, although four-membered rings are occasionally formed The chelating agent donates one or more electron pairs which it then shares with the metal ion All but the most stable metal chelates require an alkaline medium for their formation. Except for aminopolycarboxylic acids, salicylaldehyde and a few other compounds which combine to some extent with alkali metals, chelating agents react exclusively with polyvalent metal ions The only common donor atoms in chelating agents are the electronegative atoms nitrogen, oxygen and sulfur. The early development of the theory of chelation is largely credited to Werner, Ley and Pfeiffer; a recent survey of the subject has been prepared by Martel & Calvin (58).

Calcium—Calcium may be determined in serum by titration with disodium ethylenediaminetetracetate which effectively chelates calcium ion in alkaline medium (pH about 10) [Schwartzenbach *et al.* (78, 79, 80)]. In the presence of certain chelating dyes, such as Eriochrome black T or ammonium purpurate, the end point of the titration is signalized by a color change which represents the conversion of calcium-Eriochrome black T or calcium-purpurate chelate to the uncomplexed dye Ammonium purpurate possesses the advantage of specificity for calcium in the presence of magnesium Titration methods employing this reagent have been reported [Elliot (21), Greenblatt & Hartman (34)] The attractive simplicity of the method is impaired by the difficulty of obtaining a sufficiently sharp color change at the end point This disadvantage has been partly eliminated by Kibrick *et al* (45) and by Fales (23) who follow the course of titration photometrically. Fales' method appears to offer particular promise Eriochrome black T, as employed by Sobel & Hanok (82), produces a sharp end point, but as this dye also chelates with magnesium, correction for the magnesium content of the sam-

ple is necessary. This metal may be readily determined by the photometric method of Orange & Rhein (66) in which Titan yellow serves as a chromogenic chelating agent for magnesium without calcium interfering.

Heavy metals—A widely employed, exceptionally reactive, chelating agent, diphenylthiocarbazone, dithizone for short, ($C_6H_5 \cdot NH \cdot NH\ CS\ N{:}N \cdot C_6H_5$) combines with a large number of polyvalent metal ions, including those of iron, cobalt, copper, manganese, zinc, lead, mercury, bismuth, and cadmium. Advantage is taken of differences in stability of these complexes for separation of specific metals by controlling the hydrogen ion concentration At a given pH the various metal ions differ in their ability to form dithizonate chelates. Thus, mercury and copper react even in strongly acid solution whereas moderately alkaline conditions are required for lead Factors limiting more extensive application of dithizone to procedures in clinical chemistry are (*a*) the laborious preparation of the sample often necessary before treatment with dithizone, and (*b*) the relative ease of contamination of the minute quantities of metals which are usually to be measured.

The role of copper in metabolic processes has recently become the subject of considerable interest, particularly in relation to the syndrome of hepatolenticular degeneration. A simple and accurate method for estimating copper which employs sodium diethyldithiocarbamate has been reported recently [Gubler *et al* (35)] This method, which requires only 1 0 ml. of blood or plasma, should be of value in clinical studies of Wilson's disease, which is characterized by a positive copper balance As the copper excretion through the feces is greatly reduced in this condition, even an increased urinary output cannot compensate for it A very specific and even more sensitive reagent for copper is bis-cyclohexanoneoxalyl hydrazone [Nilsson (65)].

Of the many sensitive chromogenic chelating agents which have been used for the determination of iron in biological materials, the most important are o-phenanthroline [Saywell *et al.* (76)], 2,2'-bipyridyl [Jackson (42); Moss *et al* (62)], thioglycolic acid [Koenig *et al.* (47)], and catechol [Pereira (68)] Recently two new hydroxy-phenathrolines have been suggested [Hale *et al.* (36)].

Acetone and Acetoacetic Acid

The need for a method of analysis of ketone compounds of sufficient accuracy and convenience for routine laboratory application in the management of ketosis has long been recognized Of the various published procedures for their determination, none has heretofore been properly suited to the requirements of the average clinical laboratory The method of Greenberg & Lester (33) has probably been used most widely despite its lack of convenience A method which should bring the determination of ketone compounds within the scope of clinical laboratories is the elegant and simple micro-diffusion technique of Nadeau (63), who utilized Behre's salicylaldehyde reaction for acetone (6). A similar method has been reported by Bahner (3). With Nadeau's procedure, which requires no special equipment, the sum of ace-

tone and acetoacetic acid may be determined in 0 2 ml of blood in one hour. β-hydroxybutyric acid is not determined. Acetone and acetoacetic acid, contained in a measured specimen of 0 2 ml., are allowed to diffuse by evaporation from a small piece of filter paper suspended in a flask into an alkaline solution of salicylaldehyde at 50–55° C. The absorbance of the red condensation product, salicylidene-acetone, is measured at 520 mμ Readings are proportional to the concentration of acetone A minimum of processing insures against loss of acetone by volatilization This technique has been developed into a simple, roughly quantitative bedside method which can be completed within 10 minutes after withdrawal of a few drops of fingertip or venous blood [Carr & Demeny (13)] The reagent has been found to be more sensitive and specific than packaged preparations which are suitable for serum only and cannot be used with whole blood

Pentosuria

The appearance of sugars other than hexoses in the urine requires attention as the finding of reducing sugar in the urine may be erroneously interpreted and treated as diabetes A reducing carbohydrate with seven carbon atoms occurs in some varieties of avocado pears and will be excreted unchanged in the urine, it may easily be differentiated from glucose by its nonfermentability and its specific optical rotation which is +2°

More frequently, five-carbon sugars occur in the urine which are reducing, but not fermentable, and give specific pentose tests, the most popular being the Bial test with orcinol and concentrated hydrochloric acid Pentoses appear in the urine after the ingestion of fruits rich in pentose (cherries, prunes, plums, etc) and have also been recorded after the administration of certain drugs and alkaloids such as amidopyrin, pantopon, and morphine, where the pentose is supposedly derived from the glucuronic acid elaborated for detoxification of the drug Equally harmless is the occurrence of pentose in hereditary idiopathic pentosuria, an error in metabolism which makes its appearance in childhood when it should be recognized and distinguished from true diabetes mellitus The mode of its inheritance has been studied by Lasker *et al* (49) Contrary to earlier reports, in which it may have been confused with alimentary pentosuria, the pentose in these cases is L-xyloketose (L-xylulose) [Levene & La Forge (51)] In common with other keto sugars, it reduces Fehling's and similar alkaline copper solutions more readily and at lower temperatures than aldoses, reduction starting upon standing at room temperature or on mild heating

Recently, another type of pentosuria has been reported as a symptom in patients suffering from progressive muscular dystrophy and related conditions such as dystrophia myotonica, myotonia congenita and amyotonia congenita [Minot *et al* (61), Orr & Minot (67), Drew & Selving (20)] In such cases one has observed a chronic urinary excretion of a reducing pentose which forms D-ribosazone with phenylhydrazine Urine is successively treated with a yeast suspension (for the removal of fermentable sugars),

Lloyd's reagent (creatine, creatinine, and uric acid) and mercuric nitrate (glycuronates and polyphenols). To the resulting filtrate is then added a solution of phenylhydrazine. Osazone is detected by microscopy of the precipitate and, if possible, by melting point determination (156–158°).

This pentosuria is usually on such a low level that it escapes detection by the customary sugar reactions The ribosazone may also be derived from arabinose or ribulose (desoxyribose does not form osazones), but it is most likely that it originates from ribose, which is widely distributed in ribonucleic acid and its components, the ribonucleotides. These compounds can yield ribose upon hydrolysis in the course of the dystrophic process in the muscular cytoplasm. The recently discovered role of ribose as an intermediate in general carbohydrate metabolism should not be disregarded in this connection Some evidence for the presence of ribose phosphate, an intermediate breakdown product, has been obtained in these urines The analysis of urine for ribose and ribose phosphate may turn out to be of interest for the differentiation of muscular dystrophies from diseases with similar symptoms, but of neurogenic origin, and for the evaluation of the clinical state and the effect of therapeutic measures.

Serum Bilirubin

Few methods employed in clinical chemistry have undergone less change in basic principle since their introduction than the Van den Bergh test for the determination of serum bilirubin, which is an adaptation of Ehrlich's reaction with diazotized sulfanilic acid. The modification of Malloy & Evelyn (57) eliminates the loss of bilirubin which occurred with older procedures and permits quantitation of direct as well as indirect bilirubin Diazotized p-nitroaniline, stabilized as the p-toluenesulfonate, has been described as a new coupling agent for the determination of bilirubin in urine [Free & Free (27); Sobotka *et al* (86)] It is referred to as "bilazo" and is available in tablet form under the name Ictotest

Accurate standardization is perhaps the greatest difficulty in the colorimetry of the Van den Bergh test Not only is bilirubin quite expensive for routine employment, but we have found commercial preparations to vary as much as 20 per cent in regard to purity Thus, a need exists for a uniform, dependable product as a primary standard Crystalline bilirubin, obtainable from Armour and Co , appears to be satisfactory for standardization; it was found to be identical in purity with a preparation isolated from human feces, following oral administration of antibiotics [Lowry, Bossenmaier & Watson (56)]

Even with the purest of standards, owing to a systematic error in the present calculating procedure, recorded values for bilirubin are too low [Carr & Demeny (13)] Because the absorbance of the azobilirubin must be corrected for non-specific absorption, arising from other sources in the serum (other pigments, occasional turbidity), a serum blank reading is subtracted routinely from the azobilirubin reading of the corresponding serum. Undia-

zotized bilirubin in the serum blank, particularly when present in high concentrations, will contribute to the blank reading. As the reading of the serum blank is subtracted from the reading of the diazotized sample, a similar correction should be applied to the standard itself, i e the reading of an undiazotized standard solution of bilirubin should be subtracted from the reading of its diazotized counterpart No correction for this error has been applied up to the present The validity of the above conclusions is apparent from the simple treatment which follows If A = concentration of azobilirubin, B = concentration of undiazotized bilirubin, X = concentration of all other absorbing substances present, D = absorbance (optical density), then in diazotized serum (A+X) is present and in untreated serum (B+X) The difference between the absorbances of both solutions is then

$$D_{(A+X)} - D_{(B+X)} = D_A + D_X - D_B - D_X = D_A - D_B$$

The standard absorbance, which is commonly employed in calculations, is simply D_A This value must be corrected by subtracting D'_B (absorbance of undiazotized bilirubin) from D'_A in the case of the standard If this correction is not made, an error results proportional to D_B; the percentage error is $100\ D_B/(D_A - D_B)$ It varies with the concentration of bilirubin from 5 to 11 per cent Therefore, an average correction of 8 per cent should be added to the values computed without correction, or the undiazotized standard must be frequently checked and the value subtracted from that of the diazotized standard

Ketosteroids

The ketosteroids of urine, commonly referred to as 17-keto-steroids, neutral 17-ketosteroids, also as urinary androgens, have become increasingly important to the clinician in the diagnosis and treatment of a considerable number of conditions which are characterized by abnormally high or low excretions of these substances Because ketosteroids are elaborated by the adrenal cortex, the testes, and possibly the ovary, all under regulation by the pituitary gland, diseases of any of these organs usually result in abnormal excretion of ketosteroids

The normal values for adult men range from 10 to 20 mg in 24 hours, for adult women during their reproductive period, regardless of the phase of the menstrual cycle, slightly lower, say from 5 to 15 mg Children up to three years of age excrete no ketosteroids, up to eight years the upper normal limit is 2 mg, up to 12 years 5 mg, and during puberty 5 to 10 mg The values in the female menopause are normal or moderately diminished

Hypofunction of the adrenal cortex in Addison's disease, of the anterior pituitary lobe in Simmond's disease, in pituitary dwarfism, and in adenohypophyseal tumors, of the thyroid gland in myxedema, and of the gonads in some instances, is associated with low urinary ketosteroid excretion, ranging from zero in some cases of Addison's disease in women and in panhypopituitarism, to low normal values in cases of hypothyroidism. Low values may

also occur in primarily non-endocrine disorders in which the relation to testicular or adrenocortical function is not apparent. Such findings must therefore be evaluated critically [Fraser *et al.* (26)]. Moderately low values are often found in chronic disease and during the course of acute illnesses, including the common cold, the anemias, anorexia nervosa, malignancy, also in malnutrition and after marked physical fatigue It is suggested that diminished values in these cases may be a reflection of reduced adrenocortical function [Cantarow & Trumper (11)]

Conversely, increased excretion of ketosteroids is associated with hyperfunction of the adrenal cortex Cushing's syndrome, which may be a consequence of hyperplasia or tumors of the adrenal cortex or pituitary basophilism, may be associated with ketosteroid excretions varying from normal or slightly elevated levels in the majority of cases to values as high as 75 mg per day The adrenogenital syndrome is characterized by consistently higher ketosteroid excretion which includes a wide range between slightly increased values to the extremely high figure of 830 mg /day recorded in the case of a three-year-old girl with adrenal carcinoma [Engstrom *et al* (22)]

Although urinary ketosteroid levels are normally determined as the sum of the carbonyl compounds after extraction with a suitable solvent, the excretion levels of some of the constituent steroids have also been measured Dobriner *et al* (18) found that the major portion of the ketosteroids in normal urine consists of androsterone, etiocholanone, 11-hydroxyandrosterone, and 11-keto-etiocholanone The excretion of 11-oxygenated corticosteroids is markedly increased in Cushing's syndrome [Talbot *et al* (90)].

Ketosteroids may be determined by biological assay or by chemical means The most accurate method for bioassay of androgen is based upon stimulation of comb growth in the capon after topical administration of extracts of the test material to the comb for a number of days [Long (53)] Bioassay methods are difficult, expensive, and time consuming. Chemical methods for ketosteroids yield higher values than bioassay for androgens, but provide more complete information as they include the excretion of all ketosteroids without regard to differences in biological activity

Urinary ketosteroids occur as water soluble conjugates, principally as glucuronides and sulfates, which must be hydrolyzed before the free ketosteroids may be extracted with organic solvents This is achieved by acid [Dingemanse *et al* (16), Langstroth *et al* (54), Peterson *et al* (69)] or enzymatic hydrolysis [Bitman & Cohen (7), Buehler *et al* (9), Kinsella *et al* (46)] The enzyme preparations needed for hydrolysis of these conjugates are not generally available for application to routine clinical use Acid hydrolysis must therefore be employed despite the fact that destruction of ketosteroids is known to occur [Callow *et al* (10), Dingemanse & Laqueur (17), Talbot *et al.* (91)]. Conditions of acid hydrolysis must be carefully controlled in order to minimize such losses After hydrolysis, the free ketosteroids are extracted by a suitable solvent such as ether, ethyl acetate, toluene, carbon tetrachloride, or chloroform Androgens are then separated from estrogens

and other acidic substances by treatment with aqueous alkali, which forms water-soluble salts with the latter group of compounds. For most accurate work, ketones are then separated from interfering substances with Girard's reagent The purified extract is subjected to colorimetric analysis

A notable simplification in the technique of extraction and removal of interfering substances prior to analysis has been made by Drekter *et al.* (19). This technique is well adapted to the average clinical laboratory where simplicity, convenience, and adaptability to serial determination are outstanding needs The method employs a conveniently small aliquot of urine, 10 ml., and requires no special apparatus for extraction Shaking an ethylene dichloride (CH_2Cl CH_2Cl) *extract with pellets of sodium hydroxide accomplishes* removal of phenols, acids, and interfering pigments. The need for reading the final color at more than one wavelength, followed by cumbersome mathematical operations, is eliminated According to the authors, a Girard separation is not required when purification is effected in the manner described.

Colorimetric determination of ketosteroids is most frequently accomplished by the Zimmermann reaction (100) or one of its several modifications [Holtorff & Koch (41)] Critical studies of factors which influence results in this determination have been reported [Nathanson & Wilson (64), Beher & Gaebler (5)] The color reaction is sensitive to light, to reagent concentration, and to time and temperature of development. Zimmermann's *m*-dinitrobenzene reagent is by no means specific for 17-ketosteroids Not only will it react with steroids containing carbonyl groups at carbon atoms 3 and 20, but it will also produce color reactions under proper conditions with a large number of carbonyl compounds which contain CH_3 CO- or $-CH_2$ CO-groups [Carr (12)], including substances such as acetone, creatinine, and estrogens Indeed, Zimmermann's reaction is but an isolated example of a very general reaction which takes place between aromatic nitro compounds and carbonyl compounds, containing labile hydrogen atoms, in the presence of a base A degree of specificity is achieved through preliminary extraction procedures and by reading in a narrow wave band at 500 mμ where 17-ketosteroids exhibit maximum absorption while 3-ketosteroids absorb only slightly A colorimetric method for the determination of dehydroisoandrosterone and 17-ketosteroids with an anthrone reagent has been recently proposed by Graf (31)

Serum Proteins

The serum proteins are amongst the most important subjects in clinical chemistry The determination of their total quantity is accomplished by well-standardized methods, but the evaluation of the relative shares of albumin and globulin and the computation of the albumin.globulin quotient deserve a few remarks here.

These two large groups of proteins were originally defined by solubility criteria and are separated one from another in practice by their precipitabil-

ity with certain salts. The most convenient method for their separation is the precipitation of the globulins by half-saturation with ammonium sulfate which may be followed by any one of a number of analytical procedures The presence of ammonium ion precludes the determination of nitrogen by the Kjeldahl method or by Nessler's reagent. The quantitation of the total protein and of the albumin after ammonium sulfate precipitation is often carried out by Wu's colorimetric tyrosine method (97), using the reagent of Folin and Ciocalteu. The tyrosine factors are based on the tyrosine plus tryptophane content of protein fractions from normal subjects (72). They fluctuate considerably for various modifications of the method and, what is worse, deviate from normal even with one and the same modification in those very diseases where the determination of the albumin:globulin ratio is of greatest clinical interest; namely, in nephrosis and related edematous conditions with total protein values below 6 per cent and inversion of the albumin:globulin quotient. Here, the tyrosine factor of the globulin fraction increases from 16 to 20, whereas the tyrosine factor of the albumin fraction decreases from 21 to 18. In other words, the tyrosine content of globulin seems to decrease, that of the albumin to increase Similar pathological fluctuations in the amino acid composition of serum protein have been observed for cystine by Tuchman & Sobotka (92). The protein in pathological urine, generally considered as albumin, shows even greater deviations in its composition from serum albumin, with the sulfur content approaching zero [Grabfield & Prescott (30)]

In order to enable the analyst to use the Kjeldahl, Nessler, or biuret methods, separation of albumin from globulin must be accomplished by salts other than ammonium sulfate The use of sodium sulfate has some disadvantages due to the considerable temperature gradient of its saturation This obstacle may be overcome by the use of an equimolecular mixture of sodium sulfate with magnesium sulfate, recommended by Halliburton (37), or by sodium sulfite. Amongst these various alternatives the authors prefer the separation by sodium sulfite and the colorimetric biuret reaction One should be aware of the fact that in some of these separations the α-globulin stays in solution with the albumin

As will be shown further below, diagnosis often requires a more detailed analysis of the proteins. For preparative purposes further separation into subfractions may be achieved by the combined salt-alcohol precipitation methods at low temperatures, developed in Edwin J Cohn's laboratory, or by specific precipitation reactions worked out by the same school The latter methods permit the subfractionation of albumins as well as globulins.

Zone electrophoresis.—A general technique for proteins suitable for analytical ends is electrophoresis, particularly paper electrophoresis Moving boundary electrophoresis consists in the application of an electric current to a solution held in the shape of a column in a cylindrical tube, in practical performance usually U-shaped The various species of solute migrate at varying speeds, which are a function of their electric charge For technical rea-

sons, electrophoresis is carried out at low temperature near the point of maximum density of water. The results of the original procedure of Tiselius, referred to as "moving boundary electrophoresis," may be rendered by several methods They consist in photographically recording the boundaries or refractive index gradients by means of *schlieren*-optical methods; these lend themselves to the eventual planimetric evaluation of the amount of the individual fractions. As these methods are too complex for routine diagnostic purposes, we shall not dwell on them further.

Paper electrophoresis is much better suited for routine examinations as the amount of protein required is much smaller and the technique less involved. In paper electrophoresis the proteins do not migrate through free solvent, but, as indicated by the name, along a strip of filter paper imbibed with buffer These strips may be placed either in a horizontal position or folded astride a horizontal glass rod in such a manner that they form an angle of ca 20° with the vertical. In the latter method, a small volume of the protein solution is placed on the apex of the paper strip and migration towards the positive and negative pole proceeds downwards Both limbs of the strip dip into parallel troughs containing electrodes of stainless steel, platinum, or carbon The horizontal strip method employs an analogous arrangement. Either system must be kept enclosed in a suitable chamber to avoid evaporation of the solvent The chamber may be topped by a slanted roof to prevent the dripping of condensed water and to induce it to drain down the sides of the roof Some experimenters fill this chamber with an inert gas, the high heat conductance of which helps to maintain the temperature constant [McDonald (59); McDonald *et al* (60)]. In another modification the horizontal paper strip is placed between two strips of glass or plastic [Kunkel (48)]

The D C. supplied to the electrodes is usually from 200 to 500 volts and the amount from 0 1 to 3 0 milliamperes, depending on the width of the paper strip Precautions necessary for work with high voltage should be taken The empirical selection of the characteristics of the current and the details of dimension of the paper strip and of the sample will determine the speed and degree of separation and eliminate or reduce "trailing." To prevent changes of the pH on the paper strip by electrolytic phenomena at the electrodes, the latter are separated from the ends of the paper strip by a series of baffles to lengthen the path of diffusion, or by walls with perforations to minimize disturbances

In contrast to moving boundary electrophoresis, the much smaller quantities of protein used in paper electrophoresis permit complete separation of the various protein fractions into zones—hence the alternative designation "zone electrophoresis" To render them visible and evaluate them quantitatively, the strips are dried and stained Bromophenol blue, while satisfactory with the elution method, is not recommended for photometry (both to be discussed below) because of its instability when exposed to the atmosphere. Amidoblack 10 B [Grassmann *et al* (32)] and particularly Azocarmin B [Pluckthun & Gotting (70)] are most suitable for staining. The strips may

be heated to coagulate the stained protein and thus to fix it on the paper, and treated with alcohol for the same purpose and also to wash out any excess dye. Naphthalene black [Flynn & de Mayo (25)], although a useful dye, has the disadvantage that it cannot be completely washed out. The subsequent evaluation of the colored spots is based on the premise that equal amounts of the various protein fractions combine with, or adsorb, the same amount of dye This assumption is *a priori* unlikely and was shown to be incorrect in the case of Bromophenol blue, which gives a color deeper by 60 per cent with albumin than with gamma globulin; this effect is reported to be negligible for Amidoblack. Different amounts of a single protein fraction, adsorbed on the same area of paper, will not necessarily react with proportional amounts of dye or, at least, not follow Beer's Law [Crook *et al* (15)] This error is largest for the copious albumin fraction for which Crook *et al* apply a graphical correction of the photometric recording. The greater chromogenicity of this protein, referred to above, may partly compensate for this error For practical purposes, when the method is expected to yield comparative values, and, in particular, to distinguish pathological deviations from the normal pattern, one may be satisfied with the reproducibility of the results since the errors from these sources will be constant; but we shall do well in keeping them in mind, especially when we wish to compare the values with data obtained by other methods

The stained paper strips may be evaluated by cutting out the individual zones, extracting them with an appropriate solvent and colorimetrizing the resulting dye solutions [Cremer & Tiselius (14)]. Grassmann *et al* (32) demonstrated the possibility of photometrizing the paper directly. This is usually done by measuring the transmission of light in a given small area of the strip. Most authors agree that the paper should previously be rendered translucent by drenching it with mineral oil or bromonaphthalene, which approach the refractive index of paper and thus reduce its background absorption. The absorption values at regular intervals along the path of electrophoresis are then plotted on graph paper, yielding a curve which in general duplicates the electropherogram obtained by the moving boundary method; it shows the same peaks for the individual protein fractions, height and width indicating the quantity and uniformity of each fraction. But one should never lose sight of the entirely different origin and physical significance of the curves obtained by these two methods

The number of fractions, separable by moving boundary as well as by zone electrophoresis, is limited. Both albumins and globulins comprise numerous individual species of enzymes and other proteins with known and unknown physiological functions, whose behavior in electrophoresis is overshadowed by major components. Thus, a factor of uncertainty regarding the absolute quantitative evaluation of electrophoresis results cannot yet be eliminated This does not impair the comparative value of results, but it contributes to the discrepancies between moving boundary and zone electrophoresis.

Recently apparatus has been described and is becoming commercially available, which replaces the manual recording of the absorption data by scanning devices that automatically draw the absorption curve within a few minutes. The apparatus devised by Latner (50), manufactured by the American Instrument Company, uses the reflected instead of the transmitted beam of light. The relative merits of these alternatives and the selection of the proper dimensions for the slit go beyond the scope of this discussion; they have been ably treated by Crook *et al.* (15)

The final step which converts the geometrical picture into numerals is carried out by planimetry of the area below each spike. The question of how the overlap of the tails of adjacent peaks should be rigorously treated has been discussed by Crook *et al* (15), Longsworth (55), and others. The simple dropping of perpendicular lines from the bottom of the troughs of the curve is sufficiently accurate for clinical purposes The Analytrol of the Special Instrument Company automatizes this final step too by integrating the areas below the curve. The resulting relative data may then be used in conjunction with the separately determined, absolute total protein content to calculate the absolute amounts of the individual serum protein fractions

Various abnormalities in serum electropherograms have been observed in a number of pathological conditions [Longsworth *et al.* (55); Stern & Reiner (87); Sobotka (84)] In lupus erythematosus a decrease in the albumin occurs, together with an increase of the α_2- and γ-globulin fractions; the γ-globulin tends to revert to normal during administration of cortisone and ACTH, while the α_2-globulin is not affected by treatment [Reiner (71); Boas & Reiner (8)]. In multiple myeloma a variety of abnormalities is found which suggests classification of the cases in α-type, β-type, γ-type, and multiple peaks type [Reiner & Stern (73)] Other typical deviations appear in Hodgkin's disease [Rottino *et al* (75)], nephrosis, infections, and other diseases. We had the opportunity to detect a very high A/G quotient in a child, 20 years ago, before electrophoresis had become available Subsequent checks by electrophoresis indicated that the patient completely lacks the γ-globulin fraction which contains most of the antibodies [Stern & Reiner (87)]. Surprisingly enough, the girl has passed uneventfully through the usual number of children's diseases [Schick & Greenbaum (77)]. This hypogammaglobulinemia syndrome has since been recognized in a number of cases

The increasing simplification and automatization of paper electrophoresis will create in the forseeable future a body of pathological observations which in their turn promise to widen the field of application of this technique in clinical medicine.

Lipoproteins —Paper electrophoresis has a further advantage over moving boundary electrophoresis in clinical chemistry, as it enables one to determine quantitatively the lipoid portions of the several serum proteins By running a second paper strip parallel to the first one, but by drying and staining it with a lipophilic dye, one obtains a graph of the protein-bound lipoid which may be correlated, spot for spot, with strips stained for protein.

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is unlikely, as its position is nearer to the β-globulin, whereas fibrinogen approaches the γ-fraction

Quantitatively more important appears to be the fraction X (or V), travelling faster than albumin and amounting to 3 to 17 per cent of the total protein It may be a mucoprotein containing a polysaccharide component [Bauer *et al* (4)]. This point awaits further investigation along the lines indicated by Levin & Ludwig (52), who have studied the paper electrophoresis of mucoproteins in synovial fluid and umbilical cord An ultrafast fraction, X_1 [Hoch & Chanutin (40)], has been separated in a few instances from fraction X; it may be correlated with convulsive states in the patient.

Choice and Economy of Methods

The usefulness of the Clinical Chemistry Laboratory depends on the judicious choice of the items requested by the physicians According to the present state of knowledge the amount of information obtainable from the chemical laboratory varies widely amongst the various branches of medicine As the liver may well be compared to a chemical factory, no wonder that chemical tests for hepatic disease play a prominent part in blood chemistry. The items on Government hospitals' request slips are actually grouped as "Urine," "Blood Chemistry," "Liver Function Tests" The indiscriminate performance of the latter as symbolized by the expression "Battery of Liver Tests" involves much unnecessary duplication. Some of these tests are indicative of regurgitation of bile into the blood stream (total cholesterol, bilirubin or icterus index, phosphatase), the cholesterol ester determination measures the esterifying function of the liver The galactose tolerance test was found particularly sensitive to a dysfunction in arsenical and other toxic hepatitides. The increase of amino acid nitrogen in the serum at the expense of urea and the excessive excretion of tyrosine and other amino acids in the urine are indicative of a severe disruption of the deaminizing mechanism. Relatively small increases of urea, coupled with severe azotemic symptoms, should be supplemented with a serum creatinine determination, which will give a more correct picture of the degree of uremia These conditions will be observed in severe simultaneous hepatic and renal disease, also in cases of poisoning The majority of "liver tests" are "globulin stability tests" Differential significance has been attributed to the discrepancies between the thymol turbidity test and the cephalin flocculation test [Reinhold (74)], especially the Weltmann test enjoys great and continuous popularity in Europe [Wuhrmann & Wunderly (98)]. In general all these tests indicate abnormalities in the serum globulin fractions One may expect electrophoresis, if carried out serially, to furnish a scientific rationale for the outcome of these tests and possibly to supplant them altogether

We favor the concept that hepatic and renal disease express themselves by alteration of the globulin picture as far as blood proteins are concerned There are other groups of disease, less circumscribed, which affect primarily the serum albumin the malignancies, the rheumatic diseases, and the febrile

The heaviest lipoid spots are found at the same distances as the α- and β-globulins and some at the position of the albumin. In the interpretation of these results one presupposes (*a*) that the various lipoids have the same staining power, and (*b*) that the lipoprotein complexes do not dissociate during electrophoresis. Neither assumption is correct and thus the results obtained are subject to similar criticisms as the protein results There are also some non-protein-bound lipoids either originally free or liberated in the process which, because of their electroneutrality, stay at the point where the serum was originally applied to the paper.

The relative amounts of lipoid, associated with the α- and the β-fraction, vary from one species to another. The repeated feeding of cholesterol increases the β-lipoglobulins and thus lowers the α/β-lipoglobulin quotient It is the β-fraction which is enhanced in the lipemias of diabetes, nephrosis, and in particular atherosclerosis Its determination may serve as a check for therapy and as a measure for experimental regimens such as the administration of cortisone, ACTH, hyaluronidase, and heparin [Adlersberg *et al.* (85)]

Electrophoresis of cerebrospinal fluid —The total protein content of normal cerebrospinal fluid is ca. 30 mg /100 ml This is 1/200 to 1/300 that of serum and its relative distribution amongst albumin, α_1-, α_2-, β- and γ-globulin parallels in general that of serum so closely as to confirm that CSF (cerebrospinal fluid) is a physiological transudate of serum. Only in those pathological conditions, where the protein content of CSF is essentially raised, has it been possible to analyze it by moving boundary electrophoresis The more recent development of microelectrophoretic methods has made possible the electrophoresis of the protein from practically available volumes of spinal fluid in every case Most electrophoretic investigations of CSF have been done in Germany and Sweden Some of them were carried out with the interferometric electrophoresis method, but most of the work was performed by paper electrophoresis

The protein patterns of CSF in neurological conditions, where they would be expected to show significant deviations from normal, may be grouped as follows (*a*) In a great many conditions the findings remain normal, (*b*) in infectious disease, particularly in meningitis of various etiology, the products of toxic bacterial metabolism become prominent, (*c*) in demyelinating disease such as multiple sclerosis and neurosyphilis, protein fractions of neurogenic origin may be expected to increase [Wallenius (95)] The γ-globulin was found increased in the cerebrospinal fluid in multiple sclerosis [Volk *et al* (94); Yahr *et al* (99)] Whether the simultaneous increase of this fraction in the blood serum is secondary and due to permeation from the CSF into the serum, remains undecided

Two protein fractions of unexplored origin and significance have been detected in CSF by electrophoresis [Kabat *et al* (43), Fisk *et al* (24)] and seem to occur in every normal CSF The one, designated "τ" makes its appearance between the β- and γ-globulin peaks It comprises a few per cent only of the total proteins, its identity with the fibrinogen ("ϕ") of the blood plasma

out by chemists. Moreover, the taking, preservation, and transportation of blood samples is also of importance for pathological chemistry in the strict sense, whenever a more completely equipped laboratory has to perform tests on material obtained from a smaller institution or from a distant location

To estimate and to evaluate the amount of work done, or to be done, in a laboratory, it is necessary to survey the quantity and nature of the labor involved in individual tests. A mere enumeration of requests by sample or by item will give most misleading results and lead to invalid comparisons Each test may be classified according to (*a*) duration until completed, (*b*) amount of labor, (*c*) suitability for serial performance, and (*d*) technical difficulty.

(*a*) The duration of a test from the receipt of the specimen to the rendering of the result is of particular importance in cases of emergency. The rapid determination of blood sugar in suspected hypoglycemia, of calcium in convulsive states, of sodium and potassium during intravenous infusions, are cases in point Since large deviations from normal values may occur in these instances, rapidity will be the foremost guiding principle in selection of the method It is of course desirable to use the same method for emergencies and for the general routine The use of rapid methods in daily routine will make it possible to render reports the same day that the specimens have been obtained Since the blood is usually obtained before breakfast, the analysis may be finished in time to report for the evening rounds. The practice of understaffed hospitals to "do blood chemistries" every other day only should be discouraged

(*b*) Attending and resident staff should be made aware of the amount of labor involved in individual tests compared to their relative diagnostic significance The determination of the albumin/globulin quotient or a detailed protein analysis by paper electrophoresis require a multiple amount of labor in comparison to a total protein determination, the latter may be sufficient for the repeated checkups in hypoproteinemia, once the albumin/globulin ratio or protein distribution have become known Or some of the simpler globulin stability tests will offer as much information on the clinical progress of hepatic disease as a laborious serum phosphatase test or a difficult and expensive cholesterol ester analysis

(*c*) Any test that may be performed serially will save much time and labor Assume a test consists of the successive operations *m*, *n*, *o*, *p*, and *q* Assume *n* is a centrifuge run and *p* a heating period on the steam bath. These steps may be carried out simultaneously for dozens of specimens, relieving the technician during the intervening time for other tests. Obviously, the test *on a single specimen will take for completion almost as much time and disproportionally* more labor than a series The determinations of sugar by the Folin-Wu method, of urea by urease, and of cholesterol by the Bloor-Knudson method, fall into this group, where the greatest part of the time is taken up by operations which require little supervision and may be "bunched" One may add to this group the flamephotometric determination of sodium and potassium, where present day equipment requires a "warm-

infections, also pregnancy. Because of the more limited knowledge in this field some "albumin stability tests" have been mistaken for cancer tests We take a dim view of their usefulness. If tested on a population consisting of normal and of cancer patients, they often will yield promising results While they offer no sharp differentiation, they will (*a*) either take in all the malignant cases plus a number of "false positives," if small deviations from normal are considered, (*b*) or, if more rigorously interpreted, they will show up malignancies, but miss a certain proportion of "false negatives" But if tested on non-selected material they will fail, exactly where a differential diagnosis of cancer is most needed [Sobotka (83)]

Among these tests we should like to mention the heat coagulation test as developed by Glass (28), who soon recognized that the test was a measure for "severity of disease." A test proposed by Harkness (38) leads to a coefficient which is a function of the albumin/globulin/fibrinogen ratio This coefficient, while of no particular diagnostic value, is likewise a good prognostic indicator for the severity of the disease. Experimental work on serum albumin in health and disease, on its affinity for certain dyes [Westphal & Gedigk (96)] and its content of, and saturation with, fatty acids [Sher & Sobotka (81); Adlersberg *et al* (85)] will possibly lead to useful developments.

Scope and Function of the Clinical Chemistry Laboratory

The great majority of Clinical Chemistry Laboratories are operating within the framework of hospitals or as independent laboratories to serve the individual practitioner Hospitals for chronic disease such as geriatric and mental disease and tuberculosis institutions will require fewer chemical analyses per bed than hospitals for acute disease

The great increase during the recent past in service, rendered by the chemical laboratory in diagnosis, management, and control of therapeutic measures, makes it imperative for any large hospital to place its chemistry laboratory under the supervision of a qualified chemist, preferably on the doctorate level who is also a diplomate of the American Board of Clinical Chemistry This board strives for the same high standards as the various National Boards for medical specialties Any hospital of over 100 beds should have technicians specializing in chemistry at a rate of one technician for every 75 or at most 100 beds [cf Keller (44)]

A few large routine laboratories are operated by insurance companies and big industrial corporations for evaluating the health of applicants and for annual checkups on large groups of essentially healthy employees They will limit themselves to relatively few items and will select methods which lend themselves to serial analysis The choice of technique will be influenced by special situations the blood may have to be obtained by capillary puncture in the field, a small volume of blood may have to be protected against dehydration and preserved for transmission by mail While these problems and their correlation with analogous, simultaneous problems in hematology and radiology are the concern of Public Health, the techniques have to be worked

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ing-up period" of one-half hour regardless of the number of specimens to be analyzed. On the other hand, the determination of carbon dioxide or oxygen in the Van Slyke apparatus requires the undivided attention of an operator throughout every single run. Other determinations, e.g. phosphatases or keto-steroids, fall between these extremes

New analytical problems are created by the progress of clinical medicine which brings new blood constituents to the fore. Moreover, the desire to reduce the required blood volumes increases the demand for technical meticulousness. While these trends appear to be retarding factors in a technical sense, improvements in technique and apparatus as well as development of new analytical principles should be directed towards serialization Besides their economic value, serial determinations facilitate checking of the technical personnel by the frequent running of duplicates and of specimens with known amounts.

Recent Books

A number of treatises which have appeared since 1952 have been included in the bibliography Varley (93) covers clinical biochemistry in a well-organized book, which leaves the choice of several methods to the operator and supplies valuable interpretations. Stewart & Dunlop (88) emphasize the clinician's viewpoint The first volume of a series "Standard Methods of Clinical Chemistry," published by the American Association of Clinical Chemists (2), describes selected methods which have been counterchecked in at least two laboratories. Abelin (1) describes special methods of recent vintage; Hiller (39) gives a well-balanced selection of methods A few detailed monographic chapters on subjects of clinico-chemical interest will be found in the first volume of *Methods of Biochemical Analysis* (29). The blood proteins form the subject of a monograph by Wuhrmann & Wunderly (98)

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ANTIHYPERTENSIVE DRUGS[1]

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While low calorie diets, moderate salt restriction, avoidance of mental or physical strain and sedation continue to be preferred for mild cases of hypertension, there are indications that, even for the early cases, newer drugs and combinations of drugs may come to be used in the hope of postponing deterioration.

There still remain differences of opinion about the importance of reducing the blood pressure in hypertensive diseases. Some hesitate, for they regard high blood pressure as a compensatory process by which tissue nutrition is secured in the presence of contracted blood vessels Perhaps the view most widely held today is that blood pressure reduction is desirable, but that to take this far is to render the patient more susceptible to cerebral accidents and to coronary disasters; and moreover, with the substances at present available, to risk toxicity or to render the patient uncomfortable by side effects The clinical improvements which have followed effective hypotensive therapy do not support the view that high blood pressure serves ordinarily as a compensatory process; but occasionally reduction of the blood pressure to normal causes symptoms of cerebral or coronary ischemia which, however, may be dispersed in a few minutes by re-elevation of the blood pressure level.

There is evidence that high blood pressure and the associated vasoconstriction, once they have reached a sufficient degree and lasted long enough, become intermediate causes responsible for the clinical manifestations which are associated with all hypertensive diseases (1).

In such diseases as nephritis, Cushing's syndrome, aortic coarctation, pheochromocytoma, pyelonephritis, and pregnancy toxemia, the primary pathology may give rise, not only to a raised blood pressure, but also to clinical manifestations which are characteristic of the primary disorders In essential hypertension, however, the primary pathologies do not, apparently, give rise to easily recognizable clinical manifestations apart from the hypertension. It is as though the primary pathologies responsible for essential hypertension are quite innocuous except in so far as they elevate the blood pressure. While hypertension is a physical sign of a number of distinct disorders, it is also a cause, an intermediate but essential step in the development of symptomatology, of objective clinical manifestations and of certain pathological changes It is consistent with such a hypothesis to reduce and maintain the blood pressure as near to normal as is practicable with the objects of preventing further pathology and allowing recovery from reversible manifestations secondary to the raised blood pressure There is now strong evidence that the use of hypotensive drugs, if maintained in such a way as to

[1] The survey of literature pertaining to this review was completed in May, 1954.

secure a sufficient degree of blood pressure reduction for a sufficient part of the 24-hour day, leads to a considerable amelioration, often to the disappearance, of the various reversible clinical manifestations which we describe as hypertensive. This disappearance does not depend upon the nature of the original pathological process which led to the high blood pressure, *nor to an* important extent upon the means used to reduce the blood pressure so long as, in the particular patient concerned, they are effective *The improvement in hypertensive manifestations occurs equally in essential hypertension, post-pregnancy toxemia hypertension, in the hypertension of Cushing's syndrome, in nephritis of various kinds, and in the hypertension associated with renal infections, stone, etc*

The clinical conditions which may arise as the result of high blood pressure are: headache, blackouts, giddiness, breathlessness, cardiac asthma, general congestive failure, papilledema, retinal edema, soft and hard retinal exudates, retinal hemorrhages, changes in retinal arteries, angina, encephalopathic attacks, and increased susceptibility to major cerebral accidents It is usually possible before undertaking treatment to indicate which manifestations are almost certainly hypertensive, and to point to those which are likely to be relieved by lowering the blood pressure For example, with congestive heart failure, if the patient is over 70 and has only moderate hypertension benefit is uncertain; but if the patient is comparatively young and the blood pressure very high, it is usual for the patient's activity to be restored by blood pressure reduction without recourse to digitalis or other measures.

This review is concerned principally with drugs suitable in clinical practice for inducing substantial blood pressure reductions. Hence there is emphasis on methonium compounds and on the combination of methonium salts and rauwolfia alkaloids

THIOCYANATES

It is generally recognized that the hypotensive action of thiocyanates is inconstant and associated with toxic effects such as joint pains, hypothyroidism, skin rashes, and toxic psychosis In some instances small falls in the basal blood pressure occur [Alstad (2)] Subjective improvements, particularly of headache, have been reported Hoobler & Dontas (3), in their review of drug treatments in hypertension, indicate that thiocyanates have proved only a little better than placebos The drug has now been superseded

DIBENAMINE AND DIBENZYLINE

Dibenamine (N,N-dibenzyl-β-chloroethylamine hydrochloride) and dibenzyline (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride) are peripheral adrenolytic and sympatholytic substances Dibenamine is altogether too toxic for continued administration Dibenzyline has found useful clinical employment in antagonizing blood pressure crises in patients with pheochromocytoma [Allen *et al* (4)] The blood pressure falls from this

substance, given orally, do not occur in all hypertensive patients, nor are they always of substantial degree [Bakke & Williams (5); Moser *et al.* (6)] Our impression has been that the substance is too inconstant in action to be of value in the routine treatment of hypertension

Veratrum Alkaloids

The veratrum alkaloids are potent hypotensive agents [Doyle & Smirk (7), Goldman & Frierson (8); Meilman & Krayer (9); Stearns & Ellis (10)], reducing the blood pressure even of severe hypertensives to normal or to hypotensive levels, largely irrespective of the primary cause. The fall of blood pressure is associated with bradycardia Unfortunately hypotensive doses induce toxic effects, mainly vomiting, with great frequency

As the result of animal experiments, vomiting has been ascribed to a direct effect on vomiting centers [Marsh, Herring & Howard (11); Swiss (12)] This site of action is opposed by Borison & Fairbanks (13) who found, even in chronic experiments, that interruption of the vagus nerve above the nodose ganglion prevented veratrum emesis of cats The results of Swiss (12) are of clinical interest In dogs he studied the relationship between the hypotensive and emetic doses of many pure derivatives and mixed alkaloidal preparations of veratrum Equally hypotensive doses were equally likely to produce emesis, irrespective of the preparation or derivative. This is a discouraging result A new derivative with a wider gap between the hypotensive and the emetic dose may yet be found, but the expectation of success seems now to be smaller. More new veratrum derivatives are possible, for there is an amorphous material from plant sources which is hypotensive and contains unidentified substances Synthetic derivatives may be made by forming new esters without interfering much with the basic steroid structure of the substances Such synthetic bodies as have been prepared, mainly from inactive alkaloids, have not as yet exhibited useful properties.

The chief toxic manifestations in man are nausea, vomiting, retrosternal discomfort, salivation, general misery, tingling, and paresthetic sensations (14) Except for the last two manifestations there is less toxicity by the intravenous than by the oral route for equal hypotensive action. Sometimes with protoveratrine, in addition to bradycardia, there may be premature systoles and on occasion other arrhythmias [Meilman & Krayer (9, 15)]. Elek, McNair & Griffith (16), using veratrone, observed partial and complete heart block Despite the dramatic and alarming character of the toxic symptoms, death is said to be of great rarity When, however, digitalis and veratrum preparations have been used concurrently death has occurred in association with a Stokes-Adams syndrome (10) Hoobler and co-workers (17) find protoveratrine rather less toxic than mixed alkaloid preparations in equi-hypotensive doses, but meticulous dosage control is still required. Furthermore, the gap between the hypotensive and toxic doses narrows with continued administration of veratrum alkaloids [Doyle & Smirk (7); Mills & Moyer (18), Smirk & Chapman (14), Wilkins (19)] Using neogermitrine

we were unable to maintain large blood pressure falls either orally or by injection because of prohibitive toxicity (7); but small falls of blood pressure such as 30/18 might have been maintained.

There appear to be no striking differences in the therapeutic efficiency of alkavervir (Veriloid), Anatensol, Vertavis or pure neogermitrine or protoveratrine All agree that they are among the most powerful hypotensive and emetic substances known. In most patients, however, the hypotensive activity of subemetic doses is initially of modest degree and in the course of several months falls off until, in many patients, the action is little more than that of a placebo At first about one in five of our patients looked as though they would maintain a good fall indefinitely, but within two years most of them gave up. We feel protoveratrine has a very slight advantage over other veratrum products

Ergot Alkaloids

The dihydrogenated ergot alkaloids, dihydroergocornine, dihydroergocristine, and dihydroergokryptine, and a mixture of them (Hydergine), have been widely used in Europe as hypotensive agents [Hadorn (20); Kappert (21); Odenthal (22); Schimert & Zickgraf (23)]. Many authors [Bello *et al.* (24); Bechgaard & Paulsen (25); Gibbs (26); Sutton *et al.* (27)] have been unimpressed by the magnitude of the blood pressure falls induced by these substances.

Konzett & Rothlin (28) have done much to clarify further the complex action of the dihydrogenated ergot alkaloids. The alkaloids stimulate directly the plain muscle of blood vessels but, in the whole animal, this action is overcome by a combination of two effects The less important effect is a sympatholytic-adrenolytic action at sympathetic endings and the more important an inhibition of nervous centres also leading to decrease of sympathetic vascular tone. The latter action is largely medullary for, while it persists after decerebration, it is abolished in the spinal animal

Blood pressure reduction in man may follow oral administration, but injections are more effective [Bello *et al* (24), Bluntschli & Goetz (29)] It has been stated that drug toleration develops [Moister *et al.* (30)] The blood pressure fall is greater in essential than in renal hypertension [Lasch (31)] and is more conspicuous from high than from low initial levels [Kappert (21)] With large doses given parenterally postural faintness may occur [Freis and associates (32)]

The impression is that dihydrogenated ergot alkaloids, in the doses ordinarily employed, do not often maintain adequate blood pressure falls and should not be relied upon in severe hypertension

1-Hydrazinophthalazine

In animal experiments 1-hydrazinophthalazine exhibits a number of drug actions which could explain its hypotensive effect, but it is uncertain which actions determine the fall of blood pressure in hypertensive patients Taylor,

Page & Corcoran (33) report that 1-hydrazinophthalazine neutralizes the action of a pressor substance which is released from the central nervous system when the central end of the cut vagus nerve is stimulated. Schroeder (34) suggests that it may act in hypertension by abolishing the action of pherentasin (which he states is the only pressor substance consistently found in hypertensive blood) and angiotonin. Presumably some other mechanism accounts for its action in normotension. A direct action on the central nervous system has been held responsible for the blood pressure fall by Craver and associates (35, 36). A partial adrenolytic action has been suggested on the basis of smaller responses to injections of epinephrine and of norepinephrine after 1-hydrazinophthalazine has been given [Freis & Finnerty (37); Walker *et al.* (38)]. Others point to the histaminic effects of 1-hydrazinophthalazine, apparently the result of its capacity to antagonize histaminase [Meier *et al.* (39)]. The strong histamine-like reactions which occur in patients after injected or oral 1-hydrazinophthalazine are antagonized by the administration of antihistaminic substances [Hafkenschiel & Lindauer (40); Schroeder (41); Taylor *et al* (42)], and the depressor action is also diminished (43).

Blood pressure falls after intravenous injections begin in approximately 10 min (37); after oral administration in 20 to 30 min (44). To decrease side effects it has been recommended that the dose given should be increased gradually [Johnson, Freis & Schnaper (44), Wald, Fierro & Keeton (45)] It is claimed that with repeated administration side effects grow less (40, 42). In our experience, using 1-hydrazinophthalazine alone in an endeavour to secure blood pressure falls to near normal, patients were made most miserable, and we found, as others have done, that patients on this drug were unable to persist with the administration of the substance

Methonium Salts

Of the many methonium salts which have now been synthesized and tested pharmacologically, two compounds are of practical importance The use of hexamethonium in the treatment of high blood pressure was described by Restall & Smirk (46) Pentapyrrolidinium, which has been used more recently for the same purpose [Smirk (47, 48), Maxwell & Campbell (49)], is clearly the better drug and likely to displace hexamethonium.

The methonium compounds have the great advantage that in upright postures the blood pressure can be safely reduced to normotensive levels or below in about 98 per cent of hypertensive subjects Because they induce postural hypotension, however, the dose is critical and close supervision must be maintained. Postural hypotension and the occurrence of side effects attributable to parasympathetic blockade are the main disadvantages of these drugs since, as many authors are now agreed, the object of treatment is [illegible] (51), Smirk &

[illegible] Chou & de Elio (54) and of Paton & Zaimis (55, 56) showed that methonium halides blockade

autonomic ganglia. Studies on the peripheral circulation and blood pressure in normal and hypertensive individuals were made by Arnold & Rosenheim (57), who demonstrated that the blood pressure fell in the lying posture, but to a greater extent when the patient was standing The application of positive pressure to the external body surface counteracts this fall (58). An increase in the toe blood flow was observed plethysmographically [Arnold, Goetz & Rosenheim (59)], and Burt & Graham (60) found the increase in skin temperature was greater in the lower than in the upper limbs. The venous pressure also falls [Kelley, Freis & Higgins (61); Restall & Smirk (46)] After hexamethonium the blood pressure falls are much increased and *may be varied at will by the application of negative pressure to the external* body surface below nipple level [Restall & Smirk (58)] Saunders (62) found that, after small doses of hexamethonium, the application of an adjustable negative pressure to the legs makes it practicable to maintain and control hypotension. The procedure greatly lessens bleeding in neurosurgical opera- [illegible] ...stored as soon as the negative pressure

[illegible] ...mpathetic re-flexes are less active. For example, the rises of blood pressure following the *Valsalva experiment and after rapid tilt back from the vertical* to the horizontal posture are lost, and there is a decrease in the reaction to the cold pressor test.

Pentapyrrolidinium.—Pentapyrrolidinium resembles hexamethonium closely, but has a longer period of action and has at least five times the activity of hexamethonium in animals [Wien & Mason (65, 66)] and *in man* [Freis (50); Freis *et al* (67); Maxwell & Campbell (49); Smirk (47, 48)], the exact relationship depending on the degree of drug tolerance and the route of administration. Its claim to superiority over hexamethonium is that it can be given successfully by mouth in almost all patients

General remarks on the applied pharmacology of methonium compounds.—Postural hypotension occurs after giving methonium salts, the blood pressure fall being greatest when the patient is standing and comparatively little fall occurs in the lying posture with the doses which are safe for routine treatment. This explains why it is essential in *methonium treatment* to make use of posture in order to enhance the falls of blood pressure [Kuhn (68); McMichael (51), Restall & Smirk (46); Rosenheim (69), Smirk (48, 70)]. At night the patient should sit, as in a cardiac bed, or firmly propped up at 45 degrees by pillows or with the head of the bed raised on blocks 16 in high (46, 52).

[illegible] ...the of ... ael ... ad ... at ... he first, later twice weekly in conformity with a scheme which [illegible] maintenance of blood pressure reduction (48, 70)

With the methonium compounds available at present the dose is critical [Hayden (72, 75), Mackey & Shaw (76); Smirk (77); Smirk & Alstad (52)] Ten per cent above the correct dose is likely to cause postural faintness, and 10 per cent too little an inadequate fall of blood pressure. This involves a much greater degree of accuracy than is customary with dosage schemes, and for parenteral use tuberculin syringes graduated in 0.01 ml are necessary for the best results [Hayden (72); Smirk (70)].

Turner (78), who used hexamethonium orally, found the results rather unsatisfactory. Subsequent work has confirmed that, with hexamethonium salts, the effects obtained depend to an important extent on the details of the régime used, including the route of administration.

The parenteral route of administration for hexamethonium is now preferred by many authors [Doyle (79); Freis (80); Kilpatrick & Smirk (81); McMichael (51); Morrison (82); Restall & Smirk (46); Rosenheim (69); Smirk & Alstad (52)]. A "retard" preparation may be used in which 10 or 20 per cent hexamethonium bromide is dissolved in polyvinyl pyrrolidone 20 per cent, to which 1 in 2000 to 1 in 200 ephedrine hydrochloride has been added (83).

Given orally, hexamethonium bromide is probably absorbed better than the bitartrate [Harington (84)], but it should not be employed because of the risk of bromism [Holt & Litchfield (85), Locket *et al* (86), Rosenheim (87)]. With equal doses of hexamethonium ion the chloride had a slightly stronger effect than the bitartrate [Doyle (88)] Unfortunately, after drug toleration has developed, oral use of the bromide, the bitartrate or the chloride often fails to maintain adequate blood pressure falls except with prohibitive toxic reactions Failure to maintain adequate control over blood pressure levels was observed in 75 per cent of our patients on oral hexamethonium (81).

In the majority of patients oral hexamethonium should be replaced by oral pentapyrrolidinium which usually continues to be well tolerated orally, even after drug toleration has developed. Dosage, however, is critical It is necessary, for example, to employ two sizes of tablets, convenient dosage forms being a 200 mg tablet and a flat 40 mg tablet divisible into four parts, or 20 mg divisible into two parts The larger size tablets should not be divided as this involves too much dosage inaccuracy In order to obtain reproducible effects the dose should be given at a regular interval of half an hour before meals

Pentapyrrolidinium may be given by injection, a most useful preparation being a 5 per cent solution dissolved in 20 per cent polyvinyl pyrrolidone in which 0.5 per cent ephedrine hydrochloride has been dissolved to delay absorption further (48, 70) Parenteral administration is employed in the few cases where alimentary side effects such as constipation, diarrhea, or great gaseous distension do not improve with continued administration The parenteral route should be used in severe hypertensive heart failure or malignant hypertension where the blood pressure must be controlled rapidly As a rule it is desirable with twice-daily dosage at 12-hour intervals to ad-

minister a small oral supplementary dose about midday, which usually can be done without alimentary trouble even in the few patients who have had to transfer to parenteral administration.

Initial doses of methonium preparations and the increments by which they may be raised—The initial doses of various drugs and preparations used should be small, and it is best to raise the dose frequently by small increments. A suitable scheme is set out in Table I. For patients over 70 the initial doses and increments in the table should be divided by three. In patients with severe salt restriction or who have had a sympathectomy the doses should be divided by two

TABLE I

INITIAL DOSES AND DOSAGE INCREMENTS OF METHONIUM COMPOUNDS

	Initial dose (mg)		Dose may be raised by increments of (mg)		Highest final daily dose used (mg)		Average duration significant action (hours)
	As salt	As methonium ion	As salt	As methonium ion	As salt	As methonium ion	
Pentapyrrolidinium bitartrate oral	20	8 9	20	8 9	1400	623	8-12+
Pentapyrrolidinium bitartrate "retard" subcutaneous	3	1 34	0 5-1 5	0 22-0 67	140	62 3	8-12+
Hexamethonium bromide "retard" subcutaneous	20	11 2	5-10	2 8 -5 6	1200	672	3-5
Hexamethonium bromide simple aqueous subcutaneous	15	8 4	5	2 8	1200	672	2-3
Hexamethonium chloride simple aqueous subcutaneous	12	8 8	4	2 9	—		2-3
Hexamethonium bitartrate oral	187	76.1	187	76 1	9000	3663	2-4
Hexamethonium chloride oral	*125*	*92 5*	*125*	*92 5*	—		2-4

The dose is increased daily until there is an adequate effect, as judged by 3 to 6-hour control tests or by the presence of mild hypotensive symptoms in the standing posture Alternatively, when the patient is under observation in hospital, an increment may be added to each dose administered until a definite effect is obtained, this will usually mean three increments daily with hexamethonium and two increments daily with the slow-acting or oral prepa- [illegible] With oral doses a supplementary dose may be [illegible] t is to [illegible] that level which leads to mild yet unequivocal hypotensive symptoms in the standing posture Exceptionally the final dose, when drug toleration has been established, may be 20 or 30 times the recommended starting dose

Means used to discover and control the trough blood pressure (standing)—

Blood pressures taken in the standing and sitting postures at 30-minute intervals throughout the day provide the best check on the effect of a régime, and by small dose adjustments the blood pressure (standing) in the trough of the blood pressure fall can be brought down to the region of 120 systolic, with a diastolic often in the region of 90.

Casual blood pressures taken at outpatient visits are most deceptive [Alam & Smirk (89); Ayman & Goldshine (90); Freis (50); Smirk (48, 70)] During hypotensive treatment with methonium salts the blood pressure is ordinarily very labile, and patients whose blood pressures fall even to hypotension at home or during special clinic tests may exhibit intermediate or even high levels at a busy outpatient clinic (50, 70). From the level of such casual blood pressures one cannot decide readily whether dosage increases should be advised. The response of the blood pressure to a dose may be determined by tests of several hours' duration in hospital (69, 91) or in a special clinic (48, 72) or by home blood pressures (50, 90); most of our patients have had as many as 20 all-day tests Doctors in private practice may arrange days when several hypertensive patients attend for tests, blood pressures being measured by doctor or nurse. One trained person manages eight patients simultaneously.

Where no facilities exist for control tests it is far better to regulate blood pressures by the occurrence of hypotensive symptoms (48, 70) Blurred vision, dry mouth, and other mild side effects should not be allowed to limit blood pressure control but an attempt is made to lessen these in other ways. The principle of control in terms of the occurrence of symptoms can be made the same for all methonium salts, whether given orally or parenterally. In the Public Hospital, Dunedin, New Zealand, the initial dose of the drug is administered as set out in Table I. The dose is raised daily by the proper increment (Table I) until such time as the patient notices the appearance of hypotensive symptoms such as faintness in the standing posture The correct dose is one dose-increment below the dose which causes faintness in the erect posture. It is most important that mimeographed instructions are given to all patients (70) The main difficulty with control by symptoms only is that, in a few patients, even considerable hypotension produces few premonitory symptoms and the patient faints unexpectedly

Suitability of patients for methonium treatment—In general it is agreed that methonium treatment is more applicable in severe hypertension than in mild cases [Freis (92), Harington & Rosenheim (71); Kuhn (68); Palmer (93)] The following guides are satisfactory in general· (*a*) Casual blood pressures over 230/120 or basal pressures over 175/100 are usually sufficient indications for treatment even in a symptomless patient (70) (*b*) Congestive heart failure, cardiac asthma or breathlessness, hypertensive headaches, and encephalopathic or dizzy attacks are indications for treatment [Harington & Rosenheim (71), Palmer (93), Smirk & Alstad (52)] Relief from such symptoms need not be denied the elderly, but initial doses are less (70) and over 80 years they are about one-fourth of the usual for middle-aged adults

(*c*) Renal disease is no contraindication [Campbell *et al* (94), Harington & Rosenheim (71); Hayden (75); Palmer (93); Smirk & Alstad (52)] and in fact assists control over blood pressure levels by delaying drug excretion, but it must be ascertained that the blood pressure reduction does not lead to nitrogen retention. Actually it rarely does (*d*) Diplomatically and possibly for better reasons it is wiser to wait six weeks after a coronary or cerebral thrombosis before undertaking treatment. Hypotension should be avoided, and for such patients a trough blood pressure of 140 systolic in the standing posture may be sufficient reduction

Effect on clinical manifestations—Improvements in the clinical manifestations of hypertension have been reported, such as decrease or loss of papilledema, retinal edema, retinal exudates, and hemorrhages [Campbell, Graham & Maxwell (94); Harington & Rosenheim (71); Moyer, Miller & Ford (95); Murphy (96), Palmer (93); Restall & Smirk (46); Rosenheim (69); Smirk (48, 70, 97); Smirk & Alstad (52)] Such changes as disappearance of congestive heart failure and cardiac asthma, lessening of breathlessness, sometimes decrease in heart size, and improvement in the electrocardiographic picture, have been described by Doyle (79), Harington & Rosenheim (71), Kelley, Higgins & Freis (98), McMichael (51), Moyer, Miller & Ford (95), Palmer (93), Rich & Holubitsky (73), Rosenheim (69), Saville (99), Smirk (48, 70, 77, 97), and Smirk & Alstad (52). Improvements in the angina of hypertensive patients have been described [Doyle & Kilpatrick (100), Moyer *et al* (95), Rønnow-Jessen & Bech (101), Smirk & Alstad (52)] Disappearance of headaches, of dizziness and of the repetition of encephalopathic attacks have also been reported [Campbell *et al* (94); Harington & Rosenheim (71); McMichael (51); Moyer *et al* (95); Palmer (93); Rich & Holubitsky (73); Saville (99); Smirk (48, 70, 77); Smirk & Alstad (52)].

The consistency with which such improvements have been observed varies In general, with hexamethonium salts those who are prepared to employ parenteral therapy and use the effect of posture to increase blood pressure falls have reported a high incidence of objective and subjective improvement [Hayden (72), Harington & Rosenheim (71), McMichael (51), McQueen & Trewin (102), Morrison (82), Palmer (93), Restall & Smirk (46), Rosenheim (69); Smirk (97), Smirk & Alstad (52); Smirk & Chapman (14)] Where case series have been treated on oral therapy only the results reported are usually indifferent or poor [Freis & Finnerty (91), Harington & Rosenheim (71), Kilpatrick & Smirk (81), Locket *et al* (86); Mackey & Shaw (76), McQueen & Trewin (102), Turner (78)] Somewhat better results with oral therapy have been reported by Campbell & Robertson (103), Moyer *et al* (95), and Rich & Holubitsky (73)

Pentapyrrolidinium has not been widely used as yet. Effective blood pressure reduction can be secured by oral dosage in almost all patients [Freis (50); Freis *et al* (67), Maxwell & Campbell (49); Smirk (48, 70, 97)] The clinical improvements are of the same kind as with hexamethonium

salts by repeated injection. The impression has been gained that, with better control over blood pressure levels, improvement is accelerated.

Reports on the outlook as regards mortality mainly concern patients with malignant hypertension because there has not been time for a satisfactory evaluation of results in the less severe groups. In our clinic and that of the Postgraduate Medical School, Hammersmith, London, it is thought there has been an important extension of life in malignant hypertension [McMichael (104); Smirk (70, 97)] An improvement has been noted in the crude figures for Grades I, II and III hypertensives for which no statistical significance is claimed.

In certain particular instances it is likely that the patient's life has been prolonged, in that patients with advanced congestive heart failure or with severe grades of cardiac asthma have been restored to activity by the use of methonium salts in the absence of digitalis, mersalyl, salt-free diet or any other similar form of treatment

Side effects of methonium treatment—Side effects can always be eliminated, and unfortunately often are, by dose reductions which reduce active drugs to a placebo status On effective methonium therapy it is generally agreed that most patients have a few side effects The side effects occur both with parenteral and oral administration, but alimentary upsets are more prominent with the latter

The most frequent side effects are blurred vision, constipation, diarrhea, dry mouth and loss of appetite, glossitis and sore mouth, vomiting, urinary retention or delay in bladder emptying, diminution in libido and potentia Side effects do not affect all patients equally, for example, dry mouth may be present without blurred vision, or blurred vision without dry mouth With excessive dosage, constipation may progress to paralytic ileus [Bourne & Hosford (105); Lyons & Lord (106), Mackey & Shaw (107), Thomas & Williams (108)] Occasionally there is an unexpected and prolonged hypotension, usually as a result of delayed absorption of an overdose In general, side effects tend to diminish spontaneously as treatment continues [Rønnow-Jessen & Bech (101), Smirk (77)]

Parasympathetic stimulants have been used for dry mouth, loss of appetite, constipation, and blurred vision [Freis and co-workers (92, 109, 110; Smirk (70)] Suitable oral doses are pilocarpine 2 mg, carbachol 0 25 mg, or neostigmine 15 mg Blurred vision is best helped by having an extra pair of glasses, refraction being adjusted to the change in the eyes brought about by the methonium compounds Eye drops of 1/32 or 1/16 per cent of physostigmine have been helpful

Constipation is a common complaint and is met by the regular daily administration of the lowest effective dose of whatever laxative the patient finds suitable Pentapyrrolidinium is sometimes less constipating than hexamethonium [Freis (50); Freis *et al* (67), Maxwell & Campbell (49); Smirk (48, 70)], and in a few patients increases the number of bowel actions

Diminution in libido and potentia has been described [Freis (50); Freis

et al. (67); Moyer *et al.* (111); Smirk (70)]. This is more frequent after the age of 50. To minimize the symptom a reserpine-pentapyrrolidinium combination, pentapyrrolidinium or hexamethonium are to be preferred in that order. Intercourse may be timed to coincide with minimum drug action.

Injection of 100 μg. of vitamin B_{12} usually disperses glossitis and sore mouth completely (112). Urinary retention is seldom encountered to an important degree except in the early stages of treatment or when there is already some interference with micturition, as from prostatic enlargement or a neurological lesion. In such cases it is desirable to relieve obstruction, if necessary, surgically.

Reserpine

Reserpine is an active hypotensive principle of *Rauwolfia serpentina*. The presence of hypotensive activity in Rauwolfia preparations was described by Bhatia (113), Vakil (114), and Chakravarty and associates (115), and became well known through the work of Wilkins & Judson (116) A clinical study of reserpine with placebo controls was made by Löffler *et al.* (117) A mild hypotensive action followed doses of 0 75 to 1.5 mg. Side effects were usually mild, consisting of a sense of fatigue, mild mental depression, a heavy lax feeling in the limb muscles, slowing of the heart rate, and nasal congestion

When reserpine is given in doses of 2 to 4 mg. at a single dose, or as much as 9 mg. in the course of a day, considerable falls in blood pressure occur in many hypertensives [Doyle & Smirk (118)] Such blood pressure falls develop within four or five hours and are not confined to the mild and labile patients but occur in malignant hypertension and grade III types with fixed high basal pressures With such doses blood pressure falls have been as great as 138/76 on occasion 30/20 or more in 19 out of 20 patients, and exceeded 60/30 in 12 out of 20 patients Little or no postural hypotension was found

These large doses are unsuitable for routine treatment as they produce such striking side effects as gross facial flushing, nasal and conjunctival congestion with stuffiness of the nose There may be sleepiness, mental depression, occasionally mental excitement, dizziness, nausea, vomiting, and diarrhea

Mild labile hypertensives may respond well to small doses [Hensler (119); Wilkins & Judson (116)]

Combinations of Drugs

The present tendency is to use combinations of various active drugs with the objects of improving the blood pressure fall and lessening the side effects Freis (80) referred to the combination of 1-hydrazinophthalazine and parenteral hexamethonium. Good results with the combination of hexamethonium and 1-hydrazinophthalazine have been reported by Johnson, Freis & Schnaper (44), Schroeder (34), and Schroeder & Morrow (120). The experience of Grimson *et al.* (121) and of Khan (122) was unfavourable. Moyer

and co-workers (111) found the combination helpful for a time but after one year Moyer (123) reported that good results had not been maintained. Our results (43) have been discouraging.

Reports by Morrow, Schroeder & Perry (124) of delayed toxicity with the development of conditions resembling disseminated lupus erythematosus and rheumatoid arthritis suggest to us that the drug should not be used for long periods. Such important side effects are likely to occur even more frequently with continued administration

It would be well to abandon the long-term use of 1-hydrazinophthalazine alone and in combinations. The initial discomforts, the risk of collagen disorders and perhaps of blood dyscrasias [Kaufman (125)] hardly warrant its prolonged use in hypertension.

Wilkins (126), a pioneer in this field, has used reserpine with 1-hydrazinophthalazine or veratrum derivatives and on occasion a combination of several drugs He claims improved control over blood pressure levels Joiner & Kauntze (127) find the combination of a Rauwolfia preparation and veratrum offers no distinctive advantage. The results of giving reserpine and alkavervir (Veriloid) in combination were similar in our experience.

Recently trials have been made of the combination of reserpine with pentapyrrolidinium [Smirk, Doyle & McQueen (128, 129)] This so far has been the most promising hypotensive agency. In all of 40 patients equally good control over blood pressures was obtained using a reduced dose of pentapyrrolidinium or hexamethonium and side effects are usually decreased The peaks of blood pressure in between doses of methonium salts were usually much reduced, so that a more consistently low range of blood pressures is achieved Freis (50) uses a tablet containing reserpine, pentapyrrolidinium, 1-hydrazinophthalazine, and neostigmine. We prefer to keep the ingredients of a combination separate

There is little doubt that methods are now available which in careful hands allow of more substantial blood pressure reduction in hypertensives than has been practicable hitherto It remains to be seen if the clinical improvements reported on less adequate régimes will be surpassed and if the stage is set for preventive treatment in early symptomless cases

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et al. (67); Moyer *et al.* (111); Smirk (70)]. This is more frequent after the age of 50. To minimize the symptom a reserpine-pentapyrrolidinium combination, pentapyrrolidinium or hexamethonium are to be preferred in that order. Intercourse may be timed to coincide with minimum drug action.

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TOXICOLOGY[1] (ISOLATION, IDENTIFICATION AND DETERMINATION OF POISONS)

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Toxicology is a broad and poorly defined field that combines and overlaps several basic sciences. It ranges from a specialty within pharmacology through forensic medicine to the pure chemistry of poison isolation and identification. It is practiced by chemists, physiologists, pharmacologists, physicians, and others, almost at random Its scope is constantly expanded by the introduction of newer synthetic materials of economic importance (1) whose toxicity is of concern to all who may be exposed Commercial processes have increased in hazard as they were expanded Air pollution has now become a major problem in many regions (2 to 7) Pesticides, weed killers, radioactive products of atomic research (8), and many other substances must now be added to all of the newer drugs, cosmetics, and food additives that originally were the subject of the major portion of nonmedicolegal toxicology (9 to 14)

Every material, including normal physiological constituents, may be toxic under certain circumstances The large number of unusual materials to which persons are at times exposed, forces the toxicologist to determine the degree of hazard with any and all types of chemical constituents New products will continue to be tested by personnel whose main interest is in their economic value rather than in physiological effects This approach may often fail in protection of the public. Both industrial laboratories and government agencies created as a check on irresponsible manufacture and sale of new products face serious problems in recruiting properly trained personnel. Few universities in this country offer broad and thorough toxicology training, and the number of well-recognized toxicologists is so small that a university would find it difficult to recruit an adequate staff to offer such a program. The medical profession lacks specific training in the practice of toxicology, and practical considerations prohibit the ordinary physician from attempting adequate investigation of possible poisoning in his patients Research by recognized competent toxicologists is similarly restricted By comparison with most active sciences, very little high grade research is being done within the profession, though great strides in very restricted aspects of the field are being made in some industrial, government, and other laboratories

As broad as are the pharmacological and clinical aspects of toxicology, all of them finally rest on chemical methods by which the poison or its metabolic products is isolated, identified, and determined in blood or other fluids, excreta, or tissues. This chemical approach is the chief basis of practical toxicology and applies alike to the pharmacological study of toxic agents and

[1] The survey of the literature pertaining to this review was completed in July, 1954.

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marily with analysis of plant extracts or drugs, and was at times extended to the study of antihistaminics or other alkaline compounds of pharmaceutical interest (35). Such analytical studies have been performed with the ion-exchange resin IRA-400 (36) and Dowex 2 (37). Duolite C-10 and several other resins were extensively studied for alkaloid separation by Büchi & Furrer (38). Theoretical studies of ion-exchange equilibria with alkaloids were made by Saunders & Srivastava (39), while Achor & Geiling (40) recently utilized ion-exchange technique for quantitative isolation of labelled morphine from plants grown in presence of radioactive materials Perhaps the most direct application to practical toxicology was made by Levi & Farmilo (41) who made systematic studies of the determination of narcotics through ion-exchange.

As yet, no systematic approach to the general application of ion-exchange resins to poison separation has been described It would appear that with suitable arrangements to provide for removal of gross contaminants such as protein, fixed structures, and insoluble suspended material such as is common in toxicological samples, the ion-exchange method might be adapted to supplant or at least supplement the Stas and Otto separation It might even be successful in completely isolating individual poisons.

Adsorption and column partition chromatography—Adsorption of plant pigments from solution on an insoluble adsorbent was the basis of the first chromatography, and differential adsorption was also apparently the first form that was applied to alkaloids and possibly other poisons Partition chromatography in a column in which the solid serves primarily to immobilize a liquid phase is a more recent procedure but one whose technique is related closely to that of adsorption

The fact that adsorption methods may be applied to a wide variety of materials gives adsorption chromatography a unique value with some non-ionic materials that are not readily isolated by partition methods Thus, hydrocarbons and related materials from petroleum and coal tar (42) may often be isolated by use of adsorbents. When neither ion-exchange or partition methods are suitable, adsorption chromatography may often be employed advantageously

Adsorption methods have actually been widely employed in isolation of materials of toxicological significance, some of them of unusual character (43) The opium alkaloids particularly have been subjects of considerable interest, being separated usually on alumina columns (44, 45, 46) and on Florisil (synthetic magnesium silicate) (47) Other alkaloids have also been found susceptible to the same isolation technique (48 to 53). Decalso (54) and bentonite (55) have been similarly employed for complex mixtures of alkaloids. The separation of hyoscine and scopolamine (56) and of strychnine and brucine (57) on kieselguhr has been reported. Fischer & Iwanoff (58) made an extensive study of the adsorption of 115 substances including alkaloids, local anaesthetics, sedatives, plant extracts, and other materials on eight solid adsorbents and with six solvents as early as 1943. The bearing of their

to the determination of cause of death or injury as in homicide investigation The latter phase of toxicology is still concerned more with the older conventional poisons, but at present often involves newer and less common materials as well. Its methodology is partially obsolete, and a serious deficiency of trained personnel exists.

In line with the most critical function of the practical toxicologist, this review is restricted to consideration of methodology in the isolation, identification, and determination of both old and newer toxic agents. It is hoped to indicate some main lines of future research and some directions in which chemical toxicology must inevitably move in its future development Pharmacological aspects of the field will not be discussed. Several reviews and general articles covering various aspects of toxicology are available (15 to 19)

Isolation of Poisons

The first step of most toxicological investigations must ordinarily be the isolation of possibly toxic agents Historically, and to a large extent at present, some modification of the classical differential extraction method of Stas and Otto has been the most significant tool for organic poisons It is applied to tissues, blood, urine, and possibly toxic mixtures alike, which has allowed it to maintain its pre-eminent position Fundamentally, this ancient method is nonspecific and subject to interference by extraneous materials It is slow and limited in application so that it does not separate many volatile poisons and neutral organic substances Only two main groups, viz., basic materials and neutral and acidic materials may be separated cleanly. Over a period of time, numerous modifications to produce further group separations or improve the technique have been described (20, 21)

Modern methods of chromatography, ion-exchange, and electrophoresis, e g on paper, have introduced into other comparable fields the ability to make very clean, complete separations of nearly all types of materials, both similar and divergent in chemical properties, and including volatile components. Chromatography has received considerable attention in pharmaceutical analysis (22, 23), for example, in study of sulfonamides (24 to 27) and sympathomimetics (28) Paper electrophoresis similarly has been applied to drugs (29, 30) Routine applications in toxicology are still largely unexploited

Separation by ion-exchange.—Both group and individual separations are possible on columns of ion-exchange materials, and they may be adapted to small as well as to large amounts of material (31) All those substances that form ions under attainable conditions, such as alkaloids, barbiturates, and acidic or basic industrial products, are suitable for separation or isolation by this means Only the alkaloids seem to have received active study.

Early work in separating plant bases and related materials by means of ion-exchangers was reported by Mukherjee *et al* (32, 33) Similar reports by Jindra & Pohorsky (34) followed shortly This early work, as well as most that followed it even within the last two or three years, was concerned pri-

were extensively studied to separate, identify, and determine them. Other alkaloidal groups for which reports of paper chromatographic isolation or determination are available include the coca alkaloids (83), the quinine alkaloids (84) the tropane alkaloids (85), the strychnine alkaloids (50), and the solanum alkaloids (86). Of more direct interest to the toxicologist are perhaps the opium alkaloids (87, 88, 89) and in general the narcotics which have received some systematic study as a group by paper chromatography (90).

Alkaloids have been separated and determined in a variety of admixtures (91 to 96) Perhaps the most extensive systematic work in this direction has been that of Macheboeuf *et al* (97 to 101). Schute (102 to 105) has also reported a variety of studies of similar character. Jatzkewitz (106) reported procedures for determining various alkaloids and synthetic drugs utilizing paper chromatographic separation after extracting the materials from urine.

Alkaloids present fewer problems than some other groups of poisonous materials such as the glucosides which have been extensively studied, both for detecting new members of the group (107), and for the successful separation, identification, and determination of individual compounds (108 to 119). Barbiturates are much more commonly encountered because of their extensive use for suicide. Separation and individual identification by paper chromatography has been shown to be quite effective (120 to 123). Pesticides and industrial products of interest present a broad and difficult problem which may often yield to paper chromatography, and almost invariably to some form of chromatographic technique In addition to isolation, identification may also result from this approach Some illustrations of the possibilities are shown in the study of phenolic compounds (124, 125), analgesics and antipyretics (126), and aldrin and dieldrin (127)

The direct utilization of paper chromatography in toxicology has been discussed by Vitte (68) and its applications to routine narcotic analysis by Dobre & Kusafuka (90). Walker (70) was a pioneer in this country in calling attention to the possibilities of this versatile technique in toxicology as applied to law enforcement.

In addition to the limitation of small sample size, paper chromatography requires considerable preliminary fractionation to avoid an overly complex pattern and also presents the difficulty of choosing a proper set of solvents. Two-dimensional technique will assist in multicomponent systems, and ion-exchange or adsorption chromatography as a preliminary fractionation technique might be expected to solve the preliminary fractionation problem Continued research to elucidate these problems as well as choice of solvents and detection methods for the separated components is expected to modernize the practice of toxicology in the laboratory

Zone electrophoresis.—Electrophoresis, ordinarily performed on filter paper sheets as a support, is a technique somewhat newer but having much in common with paper chromatography from a technical standpoint. Instead of separating materials by means of differential solubility as in partition

investigation on toxicological practice was discussed along with practical applications Charonnat & Ormancey (59) report a study of the effect of alcohol strength on the adsorption and elution of alkaloids from alumina, bentonite, and animal charcoal (Norite)

Column partition chromatography is carried out by treating an "inert" supporting solid such as starch, cellulose powder, kieselguhr, silica gel, etc. with a solvent or solvent mixture which saturates it and charging a column with the saturated material. After adding the sample, a different and immiscible solvent or mixture is added to develop the chromatogram, acting by differential distribution of the sample between the two immiscible solvents. Fundamentally, this approach is no different from that of paper chromatography. It does have, for the toxicologist, the enormous advantage that large amounts of the material in question can be treated as compared with the small samples necessary for paper chromatography. This advantage is partially offset by the necessity of a longer and considerably more complex procedure with columns as compared with paper. A column loaded with cellulose powder is just a large paper chromatography unit, but one capable of separating a large sample with different technique of application, and particularly of detection of the separated zones.

Actual application of column partition chromatographic technique in practical toxicology appears to be infrequent. However, various types of compounds of possible toxicological interest have been isolated by this method experimentally and with considerable success, using a variety of supporting solids and solvents As illustration, a number of alkaloids have been isolated, separated, or determined (60) from solenaceous drugs (61), *Punica granatum* (62), and *Tripterygium wildfordii* (63). Glucosides have been isolated on a cellulose column (64) and phenols on silicic acid (65) Useful applications to the determination of DDT (1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)-ethane) and hexachlorocyclohexane have been made (66, 67).

Paper chromatography—Isolation by solvent partition on paper has received more attention by toxicologists than have other chromatographic procedures (68, 69, 70). This may have resulted from the widespread uses of this technique in related scientific fields combined with the relative simplicity of the method It serves both to separate small amounts of toxic agents and to make preliminary identification of them The small sample size necessary may be a limitation because it is limited to the order of a milligram This also may be a great advantage at times, and larger amounts can be separated on a column if necessary

The possibilities inherent in paper chromatography are well illustrated by its extensive use in separating numerous compounds of toxicological interest or groups, such as alkaloids, which are closely related to common poisons Plant materials have often been fractionated in this manner to define and separate the alkaloids contained in them (71, 72). Studies on the tobacco alkaloids (73, 74, 75) have been used to isolate as many as ten alkaloids or transformation products from this one source (76) Ergot alkaloids (77 to 82)

definite methods such as color tests, growth of characteristic crystals, and special chemical tests such as the Gutzeit method for arsenic.

Animal experimentation, often adopted, may indicate the mere presence of a toxic agent which is often in doubt. Sometimes, the symptoms are indicative of the poison present, and very occasionally, they may serve as proof of the individual poison. In general, recourse is taken to a variety of older identification techniques. A number of newer procedures for identification of poisonous agents have received much recent attention. These include ultraviolet and infrared adsorptiometry and x-ray diffraction, both of which are rather wide in their application, and numerous special techniques of limited application. Included as major methods for presumptive identification must be paper chromatography and electrophoresis along with the less useful column chromatographic methods.

Chromatographic and electrophoretic methods.—When the support is paper, separation by solvents or the electric current leads to a series of spots, bands, or areas, each of which contains one, or a very few components of the mixture separated. Identification of the nature of this material or materials is established (*a*) by its movement on the paper relative to that of the solvent as compared with known materials run identically (the R_F value), (*b*) by chemical tests of the material in the spot or area, and (*c*) by absorptiometric scanning methods. Sources of error in these procedures arise chiefly from the possibility that two or more materials may show the same behavior under the conditions used. Such identifications often require confirmation by independent methods before being considered final. Absorptiometric scanning is performed primarily for quantitative determination, and is limited by the absorption of the paper itself.

It is evident that location and identification of a spot or area on the paper is a portion of both paper chromatography and electrophoresis, which may allow great saving of time as compared with independent approaches to identification.

Column chromatographic methods also are useful for identification by comparison of the questioned sample with known materials eluted from the column and for quantitative analysis The method is more laborious, and requires more equipment and time, but is very suitable for some unusual types of material as discussed earlier.

A number of general references and reviews are available (128, 129, 130, 151, 152, 153) in which are discussed identification as well as separation methods by the various chromatographic and paper electrophoretic techniques Adequate identification procedures are available for nearly all of the inorganic (154, 155, 156) as well as many of the organic materials of toxicological interest (131).

Absorptiometry.—Measurements of light absorption in the visible wave lengths of the spectrum have long been familiar to the toxicologist as a means of quantitative determination of colored materials or those that can be made

chromatography, ionic constituents are separated by differential mobility in an electric field. Nonionic constituents are not affected, and negative ions move in a direction opposite to that for positive ions. Virtually nothing seems to have been done with this immensely useful and simple technique in the direct field of practical toxicology, though its apparent uses are extremely intriguing. The early emphasis on isolation of proteins and enzymes from blood serum and other sources (128 to 131) was undoubtedly attributable to the limited ability of paper chromatography to make such separations. Although there are numerous applications to nonprotein constituents (129, 130), only a few have been made to drugs (29, 30) and few if any to poisons specifically, except to the extent of inclusion of numerous metallic poisons in general systems (132). Alkaloids, barbiturates, and all of those industrial poisons that are inherently acidic or basic, along with all the drugs in the same categories should be readily separated by electrophoretic methods. Paper electrophoresis appears to offer one of the very best possibilities for isolation and preliminary identification of virtually every type of toxic agent of interest to the toxicologist, aside from a few neutral organic compounds. It is an unfortunate fact that little of this research appears to be under way in any of the toxicological laboratories, though electrodialysis for separation of groups of poisons has been described (133).

Countercurrent distribution.—This interesting technique (134, 135, 136) is a refined differential stepwise extraction, the fundamental basis of which is very similar to that of partition chromatography but capable of supplementing the results of that technique (137). It is far more complex in its instrumentation and operation than is partition chromatography, and it has consequently been used little or not at all in routine toxicological laboratories. While it is a very significant tool because of its utilization in industrial and research toxicology, in routine laboratories, it is not likely to compete seriously with the simpler techniques discussed above. It has been applied recently to tobacco (76) and a number of other alkaloidal systems (138 to 142), aromatic amines (143), cardiac glycosides (144, 145), numerous antibiotics (137, 146 to 149), and other types of materials of less direct interest to the toxicologist. Excellent reviews of this subject are available (136, 150).

Identification and Determination of Poisons

The second phase of most problems of the toxicology laboratory is the identification of a poison, usually after it has been isolated in more or less pure state. Progress in this phase of toxicology has been greater than in the relatively more difficult and critical isolation process. The success or failure of an identification is largely dependent on the efficiency of the isolation in most instances. The fact that most samples are not isolated pure, but are contaminated to a greater or less extent, often invalidates the simple and definite procedures such as physical constant determination, on which most identifications depend. The toxicologist has accordingly come to rely chiefly on less

(174), and the barbiturates (175 to 178). It should not be overlooked that most drugs in common use, including those used in doping of race horses, and a large proportion of the newer pesticides have characteristic ultraviolet absorption In fact, this is one of the very best available techniques for detection and determination of these compounds (179). The use of ultraviolet absorption in toxicology is not new, having been used by many practicing laboratories Brackett & Bradford (165) were able to assemble 69 references on this subject.

Infrared absorptiometry is far less well-known in toxicology than is ultraviolet, largely because of its later development as a practical technique, and partially because of the high cost of the infrared spectrometer Infrared radiation is absorbed by intramolecular vibrations characteristic of the various types of bonding in the molecule, e.g , carbonyl, hydroxyl, etc. groups absorb at different characteristic wave lengths Examination of an entire absorption spectrum in the infrared range allows identification and determination of the compound examined. An important limitation of the technique is the desirability of using organic solvents rather than water, but in toxicology only a few significant toxic materials are insoluble in suitable organic solvents Applications in toxicology are suggested by a limited amount of investigation with alkaloids (76, 180), a direct study of its use in toxicology in identification of barbiturates (181), analysis of mixtures of phenols and cresols (182), analysis of ointments for atropine and scopolamine salts (183), and wide application in the general organic chemistry field in elucidating the nature and structure of compounds Direct toxicological applications in the identification of an unknown antifreeze taken in dangerous quantity, and of oil of wintergreen in fatal quantities are on record A few crime detection laboratories regularly employ infrared spectroscopy for difficult and unusual organic identifications.

X-ray diffraction —Rapid strides are being made in identification and to a lesser extent, quantitative determination of certain poisonous materials by means of x-ray diffraction of powder samples which give characteristic diffraction patterns and yield very positive identifications of the crystals in the sample. The instruments are in successful operation in a number of routine laboratories (184). Limited literature references bearing directly on toxicological problems relate largely to identification of the barbiturates (185, 186) Application to this group as well as narcotics and drugs (187) and to pharmaceuticals (188) have been described The general field of x-ray diffraction in both the inorganic and organic field is very broad and comprehensive, but will not be included here

Miscellaneous techniques —In the category of quantitative determination of toxic materials a number of newer techniques are beginning to affect the practice of toxicology One of the better established of these, polarography, has been employed in a few laboratories for considerable time but has not been widely used Polarographic determination of alkaloids has been ex-

to form colored products This use is expanding constantly and is the mainstay of most laboratories for quantitative analysis, with a marked favorable tendency to adopt the spectrophotometer for the measurement Some recent procedures of this type have been published for the determination of atropine (157), yohimbine (158), alkaloids precipitable with silicotungstic acid (159) and alkaloids in general (160), cardiac glycosides (161), carbon monoxide hemoglobin (162), barbiturates (163), and other materials.

As a qualitative procedure for identification of poisons, absorptiometry in the ultraviolet, and more recently in the infrared regions of the spectrum, have developed following the general availability of adequate instruments These procedures may also be used for quantitative determination, but are beginning to find their greatest value in proof of identity of the poison, which is often of greater consequence than a knowledge of how much is present

Ultraviolet absorptiometry has received wide adoption in toxicological laboratories for both qualitative and quantitative purposes. Basically, ultraviolet absorptiometry is valuable because radiation in the wave lengths between 200 and 400 mμ is absorbed by certain groupings only, i e, those in which resonance occurs Most such groups are in aromatic or heterocyclic compounds, though this is not exclusively true. Because a very large proportion of toxic organic materials, drugs, and narcotics contain such resonating structures, ultraviolet absorption is useful throughout a wide variety of types of compound. The character of the absorption spectrum, e g, location of transmittance minima, identifies only the resonating structure present in the material, so that in many instances it will not distinguish individual compounds but only a group of compounds with similar structures, e.g, barbiturates, or morphine-type alkaloids. When the resonating structure is characteristic of one compound only, as frequently happens, the identification may be final. Some groups of similar structure, e g., barbiturates, show rapid alterations in absorption with changes in the pH, which allowed Abernethy & Siminoff (164) to distinguish between 17 different barbiturates. Probably the most extensive collection of ultraviolet absorption spectra available for toxicological purposes has been made by Brackett & Bradford (165) who employ an unconventional and very effective method of plotting transmittance data to simplify identifications. Their technique makes possible the correct qualitative and quantitative analysis with smaller quantities than have ordinarily been considered practical, though the quantities are still far greater than those that have been successfully used in analyzing other types of material with proper microabsorption cells and the Beckman DU spectrophotometer (166)

Recent studies from a standpoint primarily of identification include such toxicologically important alkaloids as strychnine and brucine (167, 168), cocaine (169, 170), and heroine mixed with procaine (171), as well as barbiturates (172) Quantitative analysis based on ultraviolet absorption has also been reported for quinine and strychnine (173), morphine and codeine

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tensively investigated (189, 190, 191), and recent work is available on thallium determination (192) and on barbiturates (193). Truffert (194) has summarized applications of polarography in toxicological analysis

Non-aqueous titration, ordinarily in acetic acid, has been effective in the determination of barbiturates (195, 196) and weak bases including alkaloids (197, 198, 199). Application to narcotics and alkaloids has been discussed by Levi, Oestreicher & Farmilo (200). Masui & Ishidate (201, 202) have described a further refinement, i.e., high frequency titration, much used in certain other analytical fields. Several new or improved reagents have been introduced of which sodium tetraphenylborate for detection and determination of alkaloids and nitrogen-containing drugs is perhaps of outstanding interest (203, 204).

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RECENT ADVANCES IN OPHTHALMOLOGY[1]

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It is not the intent of this presentation to cover the entire subject of ophthalmology. I will attempt to present the more important recent advances in the development of ophthalmic diagnosis and treatment.

LIDS AND PERIORBITA

Injuries

Painstaking examination is one of the most important factors in all traumatic injuries around the eye. It is of the utmost importance to estimate the patient's vision on first examination, even after a seemingly trivial injury While the injury to the lids or the periorbita may be perfectly obvious, one should not forget that injuries to deeper structures may also be associated.

Burns of the face and eyelids may occur from gasoline or gas explosions Lehey (1) stresses that the ophthalmologist should not fail to treat the shock which is invariably present following burns of the face and eyelids Most burns are first and second degree, although a number of third and fourth degree burns are seen The area should be covered with a sterile dressing and blebs should not be broken Most physicians feel that boric acid ointments should be avoided because of their toxicity.

A pressure dressing is of considerable value in the immediate treatment. I have found that porous, plastic-coated, absorbent, sterile dressings are of value After the dressing has been applied, a stockinette is fit over the entire face Openings are made in the stockinette for the mouth and the nose. If both eyelids are involved, the lids should be closed over the eyeball and the stockinette placed over the entire area

When the burns occur in an area from a direct flame, there may be extensive destruction in deeper structures Since it takes weeks for the slough to occur in such instances, full thickness grafts may be used to replace the area that will most likely slough The area is removed and a full thickness graft sutured to normal skin

Schofeild (2) agrees with most of this treatment but feels that immediate skin covering should be provided with split thickness graft, and every effort should be made to cover the raw lid surfaces completely. He prefers the "epithelial outlay grafts" in which the graft is much larger than would be considered necessary to cover the defect He reports 144 cases, 14 were second-degree burns, 80 were second- and third-degree burns, and 50 were third-degree burns. The majority were due to gasoline fires and explosions

[1] The survey of the literature pertaining to this review was concluded in June, 1954

Delayed plastic surgery requires considerable ingenuity. Foster (3) and others favor a pedicle flap taken from the temporal area to repair the lids Scheie (4), Spaeth (5), and others prefer the free grafts. Both techniques have advantages and disadvantages. I have found that when large grafts are used particularly for the upper lid, that the graft should be very large by comparison to the defect that needs to be filled.

Lacerations of the lids and periorbita should be taken care of almost as soon after the injury as possible, certainly within the first few days It is better to wait for the repair of the upper lid, particularly, for about 24 hr, if necessary, in order to have the repair satisfactory and meticulously done. No tissue should be lost and the edges should be brought in apposition so that contracture will be minimal. Tarsorrhaphy may be of considerable help in repairing such injuries.

Fractures of the bones that form the walls of the orbit require special consideration. It is my opinion that open reduction of these fractures should be done at the earliest possible convenience

INFECTIONS

Thygeson (6) classifies the infectious dermatoses as follows: (*a*) the pyodermas, (*b*) diseases of the sebaceous glands, (*c*) the eczema group of dermatoses, (*d*) dermatoses due to photosensitivity, and (*e*) the dermatomycoses Thygeson says that staphylococci and streptococci are associated with many of these infections It is interesting to note that Halbert and coworkers (7a) have shown that many of these organisms are antibiotic producers and may play a role in controlling the infection The roles of other organisms besides the staphylococci and streptococci are not entirely understood in lid infections There is little doubt that pityrosporum ovale is frequently associated with staphylococci on the lid. Thygeson feels that *Pityrosporum ovale* is frequently associated with seborrheic blepharitis Thygeson has also stressed that seborrheic blepharitis is frequently associated with seborrhea of the scalp and the scalp should therefore be treated as well as the blepharitis

Hordeola and chalazia are likewise complications of staphylococcal infections of the lid border. The hordeolum, or stye, is an acute furunculosis of the glands of Zeis or of Moll, situated in the lid and sometimes the hair follicle. They are frequently caused by the *Staphylococcus aureus* Pain in the lid is a frequently distressing symptom, in contradistinction to chalazion where there is little or no pain The patient may be relieved considerably by opening the stye Attempts should be made to prevent the spread of the infection to adjacent glands or lash follicles. After opening a hordeolum on the lid, it is usually wise to use one of the antibiotics The choice of the antibiotics has been covered by Braley (7b) I feel that at the present time carbomycin (Magnamycin) is probably the drug of choice to use on the lid to try to prevent spread of staphylococcal infection The second choice is probably bacitracin, and penicillin may be used locally in the form of an ointment in

the office, but penicillin should never be given to the patient. When *Pityrosporum ovale* is present, it is probably wise to use one of the ammoniated mercury preparations, or selenium disulfide may be used with care.

The mechanism for the production of chalazion, which is an inflammation in the meibomian glands of the lid, is not understood Chalazia are commonly associated with chronic blepharitis and chronic conjunctivitis There have been many interesting theories presented of recent years, particularly one by Vidal & Weil (8) in which they claim that a lipid secretion combines with the infection to produce the disorder. This oily secretion in the meibomian gland is changed and becomes a paraffin-like secretion which tends to block the necks of the glands, producing the chalazia The chalazion is a nonpainful, although uncomfortable, swelling in the lid, Occasionally these chalazia will disappear spontaneously. However, when they become red and mildly inflamed, as they sometimes do, they must be opened and the contents removed The chalazion must be curetted very carefully and all of the granulation tissue removed from the inside. If this is not done the chalazion will promptly recur.

Allergies

Allergies which occur in the conjunctiva, the lids, and, as will be seen later, also in the cornea, and probably in the deeper structures of the eye may be classified into three groups.

(a) Immediate or anaphylactic states, the response of which is edema, and is produced chiefly by inhalants; (b) Contactants, the response of which is almost always edema or eczematoid reaction, or both; (c) Bacterial hypersensitivities in which the primary response is that of eczema Bacterial hypersensitivities frequently go hand-in-hand with bacterial infections of the lids and conjunctiva Clinically, the added symptom of severe itching may be helpful.

Nearly every case of hay fever or similar inhalant allergy has a counterpart in the conjunctiva and on the lids The response of the lids is predominantly that of edema The edema of the lids may be acute and disappear rapidly in a short period of time or it may become chronic and have the appearance of an elephantiasis of the lids.

Contactants around the lids are most important. Swinny (9) thinks that the periorbital region is a frequent site of contact dermatitis He feels that the history of the contactant is the most important, whereas contact testing may be of little help. The dermatitis is most commonly an eczematoid type of reaction Cosmetics, of course, play a major role so that 85 per cent of Swinny's cases occurred in females and only 15 per cent in males Cream-base shampoos and local lotions also form an important group of contactants.

All allergies of the lids require careful history taking and examination, particularly of scrapings and smears from the lid border and conjunctiva in order to arrive at a diagnosis. While cortisone and hydrocortisone may reduce the inflammation, this does not remove the cause of the lesion I have

found that careful history taking aided by contact testing may give some leads as to further active desensitization. This is best exemplified by the report of a patient. Mrs. E. S. was a 22-year-old young lady who had had a chronic blepharitis with acute exacerbations since early childhood A pure culture of *Staphylococcus aureus* was obtained from the crusts on the lid Smears from the lids at that time showed a predominance of polymorphonuclear leukocytes with the staphylococcus and epithelial debris The response to local carbomycin was excellent and the blepharitis was completely controlled by the weekly applications of this antibiotic. Late in the spring, however, she developed a marked recurrence of the blepharitis, this time with more itching and more edema of the lids Smears from the lid border showed a predominance of eosinophils, both of which findings suggested an added allergy. No staphylococci could be found in the lid. Contact testing demonstrated a moderate sensitivity to dust. A desensitizing program was started and the response was excellent.

The physician should always be alert while treating either infections or allergies of the lid for the development of a new superimposed allergy or infection, either of which may occur during the course of treatment.

Mucocutaneous Ocular Syndrome

The volume of literature which has been built up in the past two years on this confusing subject may be divided thus (*a*) papers dealing with the etiology of this group of diseases, best exemplified by the so-called Stevens-Johnson syndrome, supporting either allergic or infectious concepts; (*b*) clinical papers dividing the syndrome into two groups, those occurring primarily on the lid (typical Stevens-Johnson disease), and those occurring primarily on the conjunctiva, such as pemphigus or some forms of erythema multiforme

Agostos and co-workers (10) in an excellent review of the entire subject of the mucocutaneous syndrome state that the theory of allergic etiology is the most tempting. They feel that drugs and bacterial products may be the sensitizing agent There is no doubt that there are many cases reported in which sulfonamides and penicillins are the incriminating agents There is a large group of authors who feel that the mucocutaneous ocular syndrome is infectious (11 to 16) Cavarra & Bietti feel that this entire group of diseases is attributable to viruses At least one disease, so-called Behçet's disease, which is a relapsing iridocyclitis with mucocutaneous lesion, has been shown to be a virus disease Sezer (17) claims to have isolated a virus from the vitreal and subretinal material of three patients The virus grew on a prepared chorio-allantoic membrane of the developing hen's egg and produced a typical encephalitis in mice. When the virus was injected into rabbits, it produced an experimental disease similar to the human disease Neutralizing antibodies and complement fixation tests were demonstrated. This work, however, has not been substantiated by other authors.

Virus Diseases of the Lids—There are a number of typical or atypical viruses which involve the lids, conjunctiva, and cornea, and many, such as

molluscum contagiosum, involve the lids primarily and secondarily involve the cornea and conjunctiva

Molluscum contagiosum and infectious papilloma or verruca are among the commonest virus lesions to involve the lid, and are frequently in or near the cilia line. When molluscum contagiosum involves the lid or the lid border, it is usually a single lesion which is pearly-white and sometimes tends to be umbilicated. They are ordinarily single tumors in contrast to the verruca or the infectious papillomas which may occur in any part of the skin of the lids These are frequently numerous and are scattered from the lid border to the brow and on the lower lid down onto the cheek.

Accidental vaccinal infections are particularly prone to occur during periods when many people are vaccinated against smallpox. Sedan and coworkers (18) had an opportunity to study several cases of accidental vaccinal infection While accidental infection is not common, they found 19 cases among 850,000 people who were vaccinated Of the 19 cases, nine involved the lids, six involved the cornea, three involved the extra-ocular muscles, and one had an iridocyclitis Accidental vaccinal infection may occur at any time even though the patient has been revaccinated a number of times Givner (19) wishes to emphasize the finger-to-eye contamination which may occur. In my experience most accidental vaccinal infections have occurred from pustules on other persons or when the patient is inoculated in a place which he may be able to reach

Herpes zoster ophthalmicus is a well-known virus disease involving the lid as a part of the inflammation of the first division of the trigeminal nerve The primary inflammation appears to be in the gasserian ganglion with secondary involvement of the skin of the lids As will be subsequently noted, not only the skin of the lids is involved but also the conjunctiva and the cornea and, many times, the deeper structures of the eye This virus disease is not well understood Strong (20) and Cavarra & Bietti (16) recently reviewed the literature There seems to be a close relationship between herpes zoster and varicella (chickenpox) but this relationship is also not understood

TUMORS OF THE EYELIDS

There are many tumors of the eyelids but one of the commonest is so-called xanthelasma. Wolff (21) feels that the region of the inner side of the eyelids have a special character of the skin and therefore are more susceptible to the presence of sebaceous cells which are likely to multiply and produce the yellow masses called xanthelasma The hair follicles are few in number in this region and since the sebaceous cells are present they grow in sheets rather than producing glands

Of course, of the other benign tumors, sebaceous and sudoriferous cysts and milium are common Gronvall (22) reviewed 375 cases of cysts which occurred around the eyelids. Most of them were sebaceous cysts and occurred most commonly in elderly people

Epitheliomas of the eyelids are common. It is generally agreed that the so-called basal-cell epithelioma occurs predominantly on the lower lid and at the inner canthus, while the squamous-cell epithelioma occurs predominantly on the upper lid. There are authorities who feel that x-ray and irradiation therapy is the treatment of choice. There are others who feel that the epitheliomas are amenable to surgery. Wakeley (23) and Ginsberg (24) used both surgery and irradiation in treatment of epitheliomas. Epithelioma of the inner canthus is the most difficult to treat since it may spread to either the upper or lower lid and invade along the inner canthus and the caruncle toward the orbit.

LACRIMAL APPARATUS

The lacrimal apparatus consists of the lacrimal gland, the puncta, canaliculi, lacrimal sac, and the nasolacrimal duct.

Tears.—Tears are a watery fluid which are present in the conjunctival sac and are a product of the lacrimal gland, the accessory lacrimal gland, the meibomian glands, and the mucous glands of the conjunctiva. DeRoetth (25) examined 827 persons and determined that the lacrimal secretion diminishes with age and begins to fall off sometime between the ages of 20 and 50 years. He concludes that the normal amount of lacrimal secretion for a particular eye is that which allows the eye to function without discomfort. He also showed that there was a tremendous variation in the amount of lacrimation in a given individual.

The enzyme lysozyme is present in fairly high concentration in tears. Smolens, Leopold & Parker (26) believe that lysozyme originates either in the lacrimal gland or from the bacterial flora of the conjunctiva. Regan (27) determined the lysozme content of human tears She found a variation of plus or minus 33 per cent of the mean lysozyme content of normal individuals. In spite of a considerable amount of research reported on lysozyme, no reason has yet been found for its presence although many suggestions have been made that it may help to control the number of bacteria in the conjunctiva.

Tearing, or epiphora, is a common complaint and has been the subject of a good deal of investigation Recently, Vouters (28) discussed epiphora associated with a normal nasolacrimal apparatus. He feels that sympathetic and parasympathetic fibers may stimulate the gland and produce epiphora. He says that psychic factors play an important part in epiphora and maintains that the control of epiphora should be done on a physiological basis

The absence of tears may be either congenital or acquired. Riley (29) documented 33 cases of congenital absence of tears. This syndrome, which occurs in children of Jewish extraction, consists of defective lacrimation, excessive perspiration, abnormal drooling, emotional instability, blotching of the skin, and motor incoordination. The absence of tears may cause corneal ulceration.

Sjögren (30) and Coverdale (31) have discussed the congenital absence of lacrimation in the past few years. Sjögren reports that there is a wide varia-

tion in the time babies develop tears; sometimes the baby never does develop tears.

The Schirmer test is the most generally used for determining the tear function While this is a rather crude test, consisting of placing a narrow strip of filter paper in the conjunctiva near the inner puncta and timing the absorption of tears by this filter paper, deRoetth (25) believes that it is still the best test. Others, such as Hudelo & Mergier (32), prefer to use strips of cigarette paper instead of filter paper.

The acquired variety of absence of tears is known as keratoconjunctivitis sicca or Sjogren's syndrome. This syndrome consists of dry eyes, dry mouth, rheumatism of the extremities, and chronic indigestion Morgan & Raven (33) have emphasized the nonocular symptoms. Since the lack of tears is only one part of the disease, they have discussed five possible factors. (*a*) The endocrine theory as to the cause of the disease, since it is commonest in females who have peculiar physical characteristics, (*b*) Avitaminosis, since these individuals seem to be chronically ill and show some suggestions of pellagra-like skin changes; (*c*) Chronic infection There has been much discussion in the past regarding bacteria and bacterial toxins producing the disease However, in many studies no bacterial or viral agent has been found; (*d*) The neurotropic factor Sjogren feels that neurogenic disturbances are almost always associated with the disease Morgan & Raven, however, are not convinced; (*e*) Heredity This may be a factor since individuals with rheumatoid arthritis and other rheumatoid diseases also have a low tear function and frequently have a dry mouth

The major clinical findings of the disease are arthritis of the hands and feet, dryness of the skin and mucous membranes, absence of perspiration, and an atrophic tongue The dryness of the vagina and loss of hair, particularly in the region of the vulva, may suggest hypothyroidism The dental changes are many times advanced, and some of the younger patients may have lost nearly all of their teeth In the digestive tract, achlorhydria and achlorylia are important findings I have not been able to find hydrochloric acid in the stomach even after the use of histamine Constipation is also troublesome and the patient's gastric crises are similar to those which occur with pernicious anemia The blood changes of Sjogren's disease are variable Some have a macrocytic hypochromic anemia. Low blood pressure is the rule. Morgan & Raven (33) have also stressed the mental changes that occur with these patients, in which they sometimes have epileptic fits I have been impressed with the fact that the mental changes come on periodically.

Treatment of the absence of tears, whether it is congenital or acquired, is most difficult. I have found that the congenital cases, particularly those described by Riley and called familial autonomic dysfunction, are prone to develop corneal ulcers unless preventive measures are taken I have found that lid adhesions or tarsorrhaphy is the treatment of choice. The cornea should be watched very closely and, if any suggestion of changes occur, lid adhesions or tarsorrhaphy should be put in at once In the case of Sjogren's

disease, or keratoconjunctivitis sicca, closing of the puncta with cautery has given some help. The physician should be sure of the diagnosis of keratoconjunctivitis sicca before recommending closure of the puncta

DISEASES OF THE COLLECTING APPARATUS

The collecting apparatus of the nasolacrimal system consists of the two puncta and canaliculi, the lacrimal sac, and the nasolacrimal duct It has been estimated by Cassady (34) and also by Cowan (35) that 73 per cent of the lumina of the nasolacrimal duct are not open at birth. Nordlow & Vennerholm (36) claim the percentage to be 67 per cent. Most ophthalmologists favor probing of the nasolacrimal duct early in infancy in order to cure the troublesome epiphora Many times infections occur during the first three to four months of life, and probing is certainly indicated. The above authors report that probing is successful 86 to 95 per cent of the time.

Atresia of the lacrimal puncta is not nearly as common. However, it did occur in 4 of 100 cases (36). From my own experience, this is not actually an atresia of the lacrimal puncta Rather the skin of the lid appears to grow over the surface of the puncta The lacrimal puncta may be found just under the surface of this epithelial layer.

Diseases of the canaliculi are sometimes inflammatory in origin in which one of the organisms of the actinomycosis group become lodged in the saccules normally found in the canaliculi. This actinomycete continues to grow and may become calcified so that the canaliculi develop what is known as a concretion Infections may be due to other organisms but it is most likely that the canaliculi become infected by dust, which carries organisms that become lodged in the canaliculi. Although it is not a common feature of the disease, the wall of the canaliculus may be invaded [Moore (37)] While expression of the concretion may be sufficient to rid the canaliculus of this infection, Moore thinks that the canaliculi should be curretted in order to get out all possible organisms.

Atresia of the canaliculi may occur either as a developmental anomaly or be acquired following inflammation The treatment is not wholly satisfactory although Henderson (38) published a number of cases in which polyethylene tubes were introduced into the canaliculi for periods of from 30 to 46 days. Following their removal many of these canaliculi remained patent Veirs (39) used nylon rods while other authors used surgical procedures to make new openings into the conjunctival sac near the inner canthus. Although some authors (38, 39) report highly gratifying results, these procedures have not been too successful in my hands. The canaliculi and other openings tend to close after a period of time

The lacrimal sac is subject to a chronic inflammation, particularly in middle-aged women. This chronic dacryocystitis is apparently caused by a partial or complete obstruction of the nasolacrimal duct. Raimondo (40) tried to explain the cause of the chronic dacryocystitis on the basis of decreased endocrine function. Since it was so common in middle-aged women

who were going through the menopause, he tried to use estrogens but without effect. Garzino (41) claims that older people have more inflammatory reaction in and around the sac This produces sclerosis and scar formation. The common findings are that older people have this added glandular dysfunction with an increase in the prevalence of bacteria in the conjunctiva. The presence of this chronic inflammation may be explained by the fact that older people tend to have more bacteria in their conjunctiva than do youngsters, possibly because of the decrease in the tear function.

Since chronic dacryocystitis is so common in middle-aged people and since it is due to the obstruction of the nasolacrimal duct, many procedures have been devised for cure of the condition. The procedures may roughly be divided into four groups: (*a*) The probing of the nasolacrimal duct, either alone or combined with the insertion of polyethylene or some similar substances, the simplest procedure; (*b*) the anastamosis of the sac to the nasal mucous membrane through the lacrimal bone; (*c*) the canalization of the nasolacrimal canal combined with a polyethylene splint; (*d*) intranasal procedures devised to combine the sac and the nose Summerskill (42) has reported extensively on the insertion of tubes into the nasolacrimal duct. He states that tubes carefully inserted will cure a large number of the cases of dacryocystitis. He feels that idiopathic dacryocystitis has a definite hereditary tendency and is probably due to a faulty development of the bony canal. When the polyethylene tube inserted in the nasolacrimal duct does not function properly, he then resorts to surgery to make a new opening between the nasal mucous membrane and medial wall of the sac. The Dupuy-Dutems procedure is probably the commonest This procedure has been subjected to numerous modifications. Several ingenious methods of tunnelization have been devised. DeJean (43) prepared a pyramidal-shaped tube of acrylic resin which he placed in the nasolacrimal canal The canal is enlarged by this procedure and the acrylic resin wedged between the sac and the nose.

CONJUNCTIVA

The conjunctiva is a mucous surface which lines the inner side of the lids and covers the eyeball to the cornea It is reflected upward and inferiorly to form the upper and the lower fornix It can be divided into the tarsal conjunctiva, the retrotarsal conjunctiva, the fornix, and the bulbar conjunctiva. Each of these areas is subject to different types of insults

The normal conjunctiva varies from birth to old age. In the newborn the major portion of the epithelium of the palpebral conjunctiva consists of a low columnar or transitional cuboidal epithelium under which is a loose connective tissue in which there are a few collections of adenoid tissue The bulbar conjunctiva consists largely of a low stratified squamous epithelium under which is a very loose areolar tissue with very little adenoid tissue From birth to adolescence the epithelium tends to become thicker and changes to a transitional epithelium but the most striking feature is the increase in the adenoid tissue. This increase in adenoid tissue may at times present itself as

a folliculosis in which there are rows of follicles on the palpebral conjunctiva. These follicles are ordinarily clear and transparent As the conjunctiva becomes more adult, the stratified squamous epithelium on the bulbar conjunctiva becomes thicker and the palpebral conjunctiva tends to become a stratified squamous epithelium. This change in the conjunctiva varies tremendously from area to area in the world. In areas where individuals are exposed to a considerable amount of dust there is more stratified squamous epithelium in the conjunctiva. In more humid areas the conjunctiva tends to remain thinner and more transparent. The normal bacteria of the conjunctiva also vary widely. Many ophthalmologists feel that the conjunctiva is normally sterile but may become contaminated by organisms that are on the lid margins and on the skin of the lid. In an urban population from 75 to 80 per cent of the people will have some organisms in their conjunctiva. In a rural population this percentage rarely reaches 50 per cent. The micrococcus or staphylococcus is found most commonly, as reported by Gibson (44). He found the micrococcus in 62 per cent of the conjunctivae. *Corynebacterium xerose* is considered by many authors as a normal inhabitant of the conjunctiva, while other authors feel that its presence in the conjunctiva is an indication of a vitamin A deficiency. It was first discovered in a patient with xerophthalmia. Gibson found bacillus xerosis in about 30 per cent. In our experience *Corynebacterium xerose* is present in less than 10 per cent of the population. It is interesting to note that the more recent publications indicate that the pneumococcus, the diplobacillus, and the streptococcus, which used to be considered as normal inhabita of the conjunctiva, are almost nonexistent in present-day cultures of normal conjunctiva. Halbert and coworkers (7a) have shown that many of these normal inhabitants of the conjunctiva are antibiotic producers. The role of organisms in the conjunctiva in stimulating adenoid tissue formation and changing the character of the conjunctiva has never been appreciated. There is no doubt that the number of bacteria in the conjunctiva increases with the age of the patient.

Of recent years there has been considerable controversy in regard to the prophylaxis of ophthalmia neonatorum. Since gonococcal infections of the conjunctiva and cornea have almost entirely disappeared, many authors would like to substitute the Credé treatment for the new born baby Mallek, Spahn & Mallek (45) compared the neonatal use of silver nitrate and penicillin in a total of 2161 births They believe that pencillin is a safe substitute for silver nitrate and that a method of administration should be selected which requires minimal handling of the infant's lids. O'Brien (46) says that ophthalmia of the newborn is the commonest form of neonatal sepsis, the incidence of conjunctivitis in infants varying from 1 to 6 per cent. There is little doubt in my mind that some modification of the Credé treatment should be instituted

Acute Conjunctivitis

Inflammations.—Acute conjunctivitis, or pinkeye, is prevalent throughout the entire world. It may or may not occur in epidemics The inflamma-

tion may be produced by bacteria or by viruses. The response of the conjunctiva to most bacterial infections is a papillary hypertrophy while that attributable to viruses is, for the most part, follicular. Of the acute bacterial infections of the conjunctiva, the pneumoccoccus (*Diplococcus pneumoniae*), the Koch-Weeks bacillus (*Hemophilus aegyptia*), and the influenza bacillus (*Hemophilus influenzae*) are the most important organisms. Tostevin (47) stated that acute bacterial conjunctivitis has a duration of from five to ten days On culture he found the Koch-Weeks bacillus and the pneumococcus the most common. He stated that the gonococcus was so rare as not to be worthy of mention.

In some parts of the world, however, severe epidemics of gonorrheal conjunctivitis do occur This is one of the chief causes of blindness in North Africa Rals (48) states that in some areas this may be combined with an acute conjunctivitis produced by the Koch-Weeks bacillus Hugonot (49) and Toulant and co-workers (50) think that the Koch-Weeks bacillus is a more important cause of the purulent conjunctivitis of North Africa. Both, however, are easily prevented or treated by local antibiotics The authors (48, 49, 50) feel that chlortetracycline or streptomycin are the most effective.

In my experience the staphylococcus may produce an acute conjunctivitis. However, it is more commonly associated with a chronic conjunctivitis Of the viruses that produce an acute conjunctivitis, the virus of epidemic keratoconjunctivitis appears to be the most important. Sporadic epidemics of this disease have occurred throughout the world The disease usually begins with edema of the conjunctiva and lids, developing into an acute follicular conjunctivitis followed by a preauricular lymphadenopathy. The disease usually subsides in from 21 to 48 days. At the present there is considerable controversy regarding the cause of the disease. While a virus has been isolated by Sanders (51), this work has not been completely substantiated, athough Sezer (52) may have isolated the virus from scrapings from the conjunctiva. Further work is necessary before the etiology can be definitely determined

Newcastle's disease —This is another interesting form of virus acute conjunctivitis. Newcastle's disease of the conjunctiva occurs in many cases where there is direct contact with chickens The disease runs a course of from 14 to 21 days. The virus is a long, slender virus which has been demonstrated from the conjunctiva by a number of authors (53 to 57)

Trachoma.—Trachoma, which must be considered as a virus disease, may either be acute or chronic The volume of world-wide literature on trachoma is enormous (58). It may begin either insidiously or acutely. Since it has a wide variety of forms, MacCallan (58) has divided trachoma into four groups The World Health Organization's expert committee on trachoma met in Geneva in March, 1952, to study trachoma and recommend therapy for eradication of the disease. They recognized the wide variation in results of therapy as well as in recognition of the disease It is widely recognized that the sulfonamides given by mouth will usually control the disease, although

even here some individuals feel that sulfonamides only control the secondary infection. The expert committee on trachoma feel that the sulfonamides, if given in proper dosage, are effective in the disease. They recognize, however, that for mass therapy chlortetracycline or oxytetracycline should better be used because of the dangers of the sulfonamides given by mouth for long periods of time. Until an absolutely certain diagnostic procedure for the diagnosis of trachoma can be obtained, there will continue to be controversy regarding the treatment of this disease throughout the world. There is no doubt of its devastating effect on the vision of individuals. In my opinion medical therapy is the most reliable. The surgical treatment should be reserved for the entropion, the trichiasis, and the shrinkage of the conjunctiva, which are common complications of the disease.

An acute conjunctivitis that is related to trachoma, in that it has inclusion bodies in the conjunctiva, is inclusion conjunctivitis. This interesting disease occurs in the new born but also may be gotten in swimming pools since it is a virus that may be found in the cervix of the female and the urethra of the male. This virus characteristically produces a follicular conjunctivitis. Ormsby and co-workers (59) have found that there is little difference in the recovery rates between sulfanilamide, chlortetracycline, and oxytetracycline There are many unusual forms of conjunctivitis reported in the literature (58).

Allergic conjunctivitis.—Since the conjunctiva is exposed to inhalants, contactants, and bacteria, it is not surprising that allergies occur. These allergies may take several forms. They may be divided into several groups; those produced by inhalants and contactants, those produced by bacteria and bacterial toxins, the atopic type, and a group of unknown allergic conjunctivitis This latter group is best exemplified by so-called vernal conjunctivitis, the conjunctivitis which begins in childhood as a disease of the spring, summer, and autumn It produces a severe conjunctival reaction in the form of large cobblestone papillae.

The acute allergic conjunctivitis produced by inhalants is an immediate response. Pollen, dust, dander, feathers, and food produce this conjunctivitis. It is associated with a milky discharge from the conjunctiva, and the conjunctival surface is pale and covered with fine papillae. Hanser and coworkers (60, 61) have shown that eosinophils are a prominent feature of this disease and the number of eosinophils will increase as the symptoms increase.

The allergic dermatoconjunctivitis, which is sometimes associated with an eczematoid dermatitis of the skin of the lid, is usually a delayed allergic response produced by such important allergens as locally applied drugs (atropine, scopolamine), cosmetics, and wearing apparel. In contradistinction to the acute allergic conjunctivitis, the conjunctiva in this type is usually red and inflamed Eosinophils may or may not be apparent in the scrapings. Theodore (62) thinks that ocular drug intolerances are important in the development of drug allergies Many of these drugs act as irritants,

particularly if they deteriorate in solution, and their degenerative products act as adjuvants in sensitizing the conjunctiva If the drug irritant can be recognized early enough, sometimes a drug allergy can be prevented. This is particularly true if the drugs are carefully compounded.

Chronic allergic conjunctivitis is usually considered to be of two types: the atopic, which has been described by Hogan (63), and the delayed bacterial type. This latter group may show an allergic response to bacteria, fungi, and possibly viruses The atopic allergic conjunctivitis is so typical, Hogan states, that the entity deserves a specific title of atopic keratoconjunctivitis. The atopic individual is sensitized during infancy. It is an immediate reaction to the sensitizing agent The conjunctivitis is associated with burning and mucoid secretion Remissions and exacerbations are common Secondary infections with staphyloccocci occur.

The bacterial, or delayed type of allergic conjunctivitis, has been more difficult to evaluate The outstanding example of the bacterial allergy is phlyctenular keratoconjunctivitis The volume of literature on phlyctenular conjunctivitis is enormous (64 to 67) Thygeson (68) has shown that phlyctenular keratoconjunctivitis is almost entirely an allergy to tuberculoprotein. He states that on rare occasions there may be an allergy either to bacterial, viral, or fungous infections. Numerous authors feel that the pneumococcus and Koch-Weeks conjunctivitis may have an associated phlyctenular allergy. Thygeson (68) says that these two organisms are very low sensitizers and it may be that these organisms act as a trigger mechanism to produce the sensitization to the tuberculoprotein He has also demonstrated that the staphylococcus is capable of producing a phlyctenular-type lesion in the eye The great majority of cases, however, are certainly produced by tuberculoprotein

Unusual forms of conjunctivitis —Parinaud's conjunctivitis has always been of interest to ophthalmologists since it represents a granulomatous type of inflammation of the conjunctiva associated with lymphadenopathy Recently, numerous references have been made to a so-called cat-scratch fever which may or may not be associated with a conjunctivitis (69 to 73). This disease has been called benign infectious lymphoreticulosis and it has been suggested that it is a virus disease An antigen was prepared by Daniels & MacMurray (69) from a lymph node The antigen gave positive reactions in patients with the disease Ridley & Smith (74), however, isolated the leptothrix from one of the suppurative preauricular lymph nodes The organism was similar to the one isolated by Verhoff & King several years ago. However, it did not ferment sugars as readily Cassady & Culbertson (75) presented an excellent review of the literature, including four cases, all of whom were sensitive to Daniels' and MacMurray's cat-scratch fever antigen. Since that time Cassady has had an opportunity (personal communication) to test many of the patients who had typical leptothrix infection and found that they too were sensitive to the antigen prepared by Daniels & MacMurray Since the leptothrix is a difficult organism to grow,

it is certainly possible that cat-scratch fever and leptothrix oculoglandular syndrome are one and the same disease. They certainly are clinically identical. The leptothrix described by Ridley & Smith and also by Verhoff & King are frequent inhabitants of the fur and mouth of cats.

CORNEA

Anatomically, the cornea consists of the epithelium, Bowman's membrane, the corneal stroma, Descemet's membrane, and the endothelium. Diseases of the cornea may be classified as hereditary, developmental diseases, infections, allergies, and degenerations. The volume of literature on diseases of the cornea is enormous (76).

Guild, Walsh & Hoover (77), Kennedy (78), and others have reported on the demonstration of cystine crystals in the cornea. Since this is an inborn error in metabolism and is hereditary, the cystine crystals are deposited in the cornea as well as in other organs. The metabolic block in cystinuria is a failure in the oxidation of cysteine to a sulfate. This causes its precursor, cystine, to accumulate in body fluids The cystine crystals accumulate in the conjunctiva and in the cornea and may be seen with the slit lamp microscope.

One of the most important problems for experimental work that has been done in the recent years has been on corneal transparency. Research on the problem of corneal transparency has taken several angles. Teng & Katzin (79) have demonstrated the presence of a fine basement membrane, distinguishable from Bowman's membrane, which is between the epithelial layers and Bowman's membrane It varies in thickness and width from one-third the thickness of Bowman's membrane to considerably less. This membrane may have something to do with the epithelium sticking tightly to the stroma One approach to the transparency of the cornea has been the presence of corneal mucoid. There has been a considerable difference between the corneal mucoid of fish and that of mammalia since the fish cornea swells much less in water than does the mammalian cornea (76). Aurell & Holmgren (80), using metachromatic staining, demonstrated that the collagen fibers of the cornea absorbed a good deal of metachromatic substance The pronounced capacity of the swelling of the cornea in water, which had been demonstrated by them before, is a characteristic which chiefly resides in the stroma of the cornea. These authors feel that the mucoid content of the collagen fibers of the stroma absorb the water. Smelser & Ozanics (81) have demonstrated that a corneal haze develops after the wearing of contact lenses This haze increases the corneal thickness, which is present in the stroma. The authors demonstrated that the glycogen stores of the cornea were rapidly exhausted when contact lenses were worn, and that this may produce the swelling. They feel that when the glycogen reserve is exhausted, water enters the cornea more rapidly than it can be removed Bock & Maumenee (82) by an ingenious experiment showed that diffusion across the cornea to and from the aqueous of substances vital to this tissue are essential to the

survival of the stromal cells. They feel that osmotic forces act through the epithelium and endothelium as semipermeable membranes, but that they are not solely responsible for keeping the cornea clear. Potts (83) feels that the present accepted theories of corneal dehydration should be revised. He states that the epithelium of the cornea is relatively impermeable to most substances while the endothelium is, relatively, permeable to salt. The aqueous supplies much of the nutrition to the cornea All of these experiments would indicate that much further work is necesssary in order to decide how the cornea remains clear. There is no doubt that the corneal mucoid and the detergesence of the corneal stroma are important factors in maintaining the transparency.

Thygeson (84), Gundersen (76), and Braley (85) feel that there has been an increase in the number of cases of herpes corneae in the United States since World War II. Herpes corneae has not been a severe disease Thygeson (84) and Gundersen (76) say that, prior to the advent of cortisone, corneal perforation was an unheard of complication of herpes corneae and hypopyon was exceedingly rare Both warn against the use of cortisone or hydrocortisone in the treatment of herpes corneae. In personal communications between these two authors, they state that cortisone and hydrocortisone may help to cause the development of herpes corneae Gunderson (76) says that, in spite of the fact that herpetic patients often feel more comfortable while taking cortisone and that a few isolated favorable reports have appeared, only harm can be expected from its widespread use The best form of therapy still seems to be the removal of the corneal epithelium and the cauterization with 3½ per cent tincture of iodine

Central ulcers —At the present time central ulcers of the cornea are very likely to be caused by *Pseudomonas aeruginosa* This common saprophyte produces a devastating ulcer of the cornea The organism sometimes gains access to the cornea following an abrasion or the removal of a corneal foreign body, or it may be introduced into the eye from soil or from contaminated solution Diagnosis is sometimes difficult unless immediate smears and cultures are made from the cornea. There have been a number of cases of pyocyaneus ulcers of the cornea which have been produced by the use of contaminated cortisone and fluorescein solution Unless the eye is treated within the first 24 hr., it may be lost The treatment depends upon sensitivity tests, although polymyxin B, chloramphenicol, and streptomycin appear to be the most valuable antibiotics Of the chemotherapeutic agents the sulfonamides are sometimes more effective than the antibiotics Eareckson, Miller & Long (86) report a case in which the diagnosis of the corneal infection was *Pseudomonas aeruginosa* and treated with polymyxin B and varidase The authors feel that the combination of the two is better than the use of polvmyxin B alone. They are of the opinion that the thick mucopurulent material, which is present in the cornea, prevents effective antibiotic action and that varidase is a tool to remove the fibrin and pus Klein & Millwood (87) contend that pyocyaneus infections of the cornea are better controlled by the use of gelatin

disks impregnated with streptomycin. They recommend the early use of these impregnated caps and disks in first-aid stations of industrial plants as an effective preventive of an infection following traumatic injuries to the cornea. I have always used local 7½ per cent gantrisin as an ointment or as a drop in the eye in an effort to prevent this dangerous infection.

Thygeson, Hogan, & Kimura (88) have reviewed the role of cortisone in bacterial as well as non-bacterial keratitis They have reported an extensive review of the literature Both cortisone and hydrocortisone have great value in ocular diseases arising from all types of allergies. This is particularly true of bacterial allergies. Cortisone and hydrocortisone are effective therapy, according to these authors, in cases of phlyctenulosis, in non-granulomatous uveitis, and in marginal infiltrations or ulcers of the cornea. These hormones are also extremely effective in most types of rosacea keratitis Drews, Barton & Mikkelsen (89) present an excellent review of a study which extended from 1944 to 1950, in which 90 patients were treated for acute interstitial keratitis. During this period penicillin alone or in combination with arsenicals and bismuth had no significant effect on the course of interstitial keratitis They report, however, 18 patients who were given hourly instillations of 2½ per cent cortisone drops in the eye while they were being treated with penicillin intramuscularly. Pain and photophobia were relieved within three to four days and, in all but two cases, there was clearing of the cornea. A final vision of 20/20 or better was obtained in 26 of the 29 eyes treated. Three patients experienced a recurrence after cortisone was discontinued; however, each responded as soon as cortisone treatment was resumed.

The literature on keratoplasties of the cornea occupies a very large portion of the ophthalmic literature In spite of this relatively few cases of corneal transplant have been done in the entire world. The results in this period over previous periods reported have not shown a striking improvement. Lamellar keratoplasty has occupied a more favorable position

With the increased interest in collagen diseases, the fibrous coats of the eye, the sclera and the cornea, show similar changes. Polyarteritis nodosa, erythema nodosa, and scleratomalacia are all of interest. Goar & Smith (90) presented two interesting histological cases. They describe polyarteritis nodosa of the eye as a focal degenerative inflammatory disease of the small and medium sized arteries characterized by a peculiar type of hyaline-like necrosis which is called fibrinoid degeneration. Around these areas the cells show active acute inflammation The changes occur in the vessels of the sclera, the choroid, and occasionally in the retinal, ciliary, and vessels of the extra-ocular muscles Kartka (91), Boehringer (92), and Francois (93) have stressed the collagen nature of all of these diseases and have described the necrosis and sequestration of the sclera with the associated necrosis. Rheumatoid arthritis may be an associated disease

THE LENS

While there has been a considerable amount of work done on the lens and the lens structure, very little new has been added in the past several years.

The publication in *Science* (94) of the non-surgical treatment of cataracts which received wide notice in the lay press, was unfortunate The alleged beneficial effect on cataracts of parenteral injection of a preparation of fish lens protein caused widespread interest, but the report of the subcommittee of the National Research Council concluded that no adequate evidence was available to show that the fish lens protein had any effect The committee suggested that no further investigation of this treatment should be conducted because of its past proven ineffectiveness and because it was potentially dangerous to the patient (95) Although periodically non-surgical treatments for cataracts are bound to appear, to date there is no proof of any beneficial effect.

The Ridley lens (96) has aroused a considerable amount of attention, not only in this country but in Europe. This ingenious and dramatic operation consists of replacing the cataract with an intraocular, clear, acrylic resin, plastic lens. Numerous successful operations have been reported by a number of authors (97) Most authors, however, urge caution and some have cited dangers of postoperative infection, later dislocation, and foreign body reaction.

Research on experimental cataracts has continued over a period of many years so that the carbohydrate cataracts have been studied as extensively as have those of the alloxan diabetic cataracts. The galactose cataracts were reported by Patz (98) and Steiner (99). Both have studied the galactose cataracts extensively in children The galactose cataracts are reversible until the opacities become complete Improvement is often remarkable on a milk-free diet which may result in complete recession of the cataract while the lens remain clear. Craig & Maddox (100) showed that feeding high galactose diets to rats produced cataracts in from 9 to 20 days

Radiation cataracts have attracted the attention of many physicians. Alter & Leinfelder (101), studying the effects on rabbits' lenses, demonstrated that the lens could be shielded and cataracts prevented with a low dosage irradiation, provided the equatorial region of the lens could be protected. Ham (102) described cataracts caused by the cyclotron, the atom bomb, and accidental nuclear reaction cataracts in humans, and has published an extensive review of the literature

DISEASE OF THE UVEAL TRACT

The uveal tract is the vascular coat of the eye It consists of the iris, the ciliary body, and the choroid The mesh work of the iris angle, which forms the drainage system that covers the scleral furrow between the cornea and sclera in front of Schlemm's canal, may be considered as part of this uveal structure. There has been considerable interest in some of the congenital or developmental anomalies of the iris and chamber angle A good deal of this interest has been aroused by Barkan (103) Barkan has demonstrated to his satisfaction that, because of the glaucoma in congenital aniridia, there is a persistent embryonic tissue in the angle which pulls the rudimentary root of the iris toward the line of Schwalbe, thus sealing off the angle from the cham-

ber. He feels that a similar process is the cause of typical congenital glaucoma. We (104, 105) feel that this is not a persisent embryonic tissue that pulls the iris forward in either congenital glaucoma or in aniridia but rather a failure of the opening of the chamber angle due to incomplete cleavage between the portions of the uveal tissue that makes up the chamber angle. Barkan's (103) treatment of the condition is an attempt to open the chamber angle by goniotomy and appears to be the preferred treatment.

Of recent years there have been a number of studies conducted on choroideremia which has been recently reviewed by Sorsby and co-workers (106). In males the condition is progressive and, while the patients are born with pigment, it slowly disappears from the choroid In females, although the ophthalmoscopic changes are marked, there are no subjective symptoms and there is no progression of the disease. An affected male will have a mother who shows the carrier state. Since women carriers can be identified the condition can be diagnosed by the study of only two generations The authors wish to change the name from choroideremia to progressive choroidal atrophy. A large number of families have been studied in the United States and Canada of recent years, and this important disease has aroused considerably more interest than has retinitis pigmentosa, which is known to be hereditary.

The volume of literature on diseases of the uveal tract has been adequately covered by Hogan (107) and Calhoun (108).

The most interesting inflammatory disease of the uveal tract studied in recent years is toxoplasmosis. In the past it was believed that this interesting chorio-retinal lesion occurred only "in utero" but the findings of Hogan, Thygeson & Kimura (109) have changed this view Busacca and associates (110), Wegmann & Gut (111) and Koke (112) have confirmed that toxoplasmosis may produce a chorioretinopathy in the adult. While the toxoplasmic antigen and complement-fixation tests are not entirely accurate, the methylene blue dye test is the most reliable test for toxoplasmosis Busacca and associates (110) reported 28 5 per cent positive results in adult patients *with active chorioretinitis, whereas, when the same test* was performed on controlled patients without chorioretinitis, he found only 3 per cent positives At the recent meeting of the Association for Research in Ophthalmology in San Francisco, considerable more evidence was presented to indicate that adult infection does occur

Sympathetic ophthalmia —Evidences to support the two theories of sympathetic ophthalmia are still being presented. Collins (113) has continued his work, using adjuvants combined with uveal pigment The adjuvants were aquaphor, liquid petrolatum, and heat-killed tubercle bacilli This work would suggest that sympathetic ophthalmia is due to a bacterial hypersensitivity or a sensitivity to uveal pigment in which bacterial substances act as the adjuvant

Schreck (114), however, believes that the chicken represents a natural reservoir for a virus which is the cause of sympathetic ophthalmia. Schreck's work has been substantiated by Redslob (115) *They claim that this ultra-*

microscopic virus has an affinity for uveal tissue but travels from the first eye along the retinal vessels to the chiasm and then up the second optic nerve to involve the second eye In a recent panel discussion of virus diseases, several virologists were of the opinion that since no one except Redslob had been able to substantiate Schreck's work and he used the same type of chickens, it was the majority opinion that Schreck and Redslob were stimulating a latent virus in the chicken.

There are numerous reports in the literature regarding the excellent effects of cortisone and hydrocortisone on sympathetic ophthalmia. No doubt the inflammation can be decreased by the use of ACTH or cortisone when given either intramuscularly, intravenously, or by mouth, but I have not been favorably impressed with its ability to prevent complete loss of sight once the disease is definitely established.

GLAUCOMA

The glaucomas may be divided into the primary glaucoma, in which there is no apparent cause for the development of the elevated intraocular pressure, and the secondary glaucomas, where there appears to be some cause for the glaucoma. Congenital glaucoma has been previously discussed under uveal tract.

The present conception of the primary glaucomas can be divided into two large groups the narrow angle glaucoma and the wide angle glaucoma. Scheie (116) and Haas (117) have covered the literature on glaucoma completely and have presented a very complete classification of the disease, including the diagnosis, the medical management, and the surgical management.

Little has been added in recent years to the medical therapy of glaucoma. The usual miotics are still useful in treating glaucoma. It has been shown by tonography studies that glaucoma is undoubtedly a disease in which the elevation in the intraocular pressure is due to a partial obstruction of the outflow at the chamber angle Pilocarpine and the other miotics seem to increase this outflow of aqueous from the anterior chamber.

Becker (118), however, has presented the most interesting theories in regard to glaucoma By the giving of Diamox (Acetazoleamide), Becker was able to reduce intraocular pressure considerably Diamox is a sulfonamide which inhibits carbonic anhydrase and effectively decreases the intraocular pressure Subsequent studies have shown that it probably reduces the flow of aqueous into the eye Pressures can be remarkably reduced in from 60 to 90 min with a maximum effect in from 3 to 4 hr after an initial dose of 500 to 1000 mg In some instances the pressure was over 60 before Diamox, reduced to 25-27 after its administration Patients have been maintained on Diamox for six months I have found that it reduces the pressure in most cases of glaucoma although an occasional case may not respond favorably. The side effects are marked diuresis and, after a period of time, diarrhea is prominent. The diarrhea sometimes can be controlled by reducing

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Of recent years there have been a number of studies conducted on choroideremia which has been recently reviewed by Sorsby and co-workers (106). In males the condition is progressive and, while the patients are born with pigment, it slowly disappears from the choroid. In females, although the ophthalmoscopic changes are marked, there are no subjective symptoms and there is no progression of the disease. An affected male will have a mother who shows the carrier state. Since women carriers can be identified the condition can be diagnosed by the study of only two generations. The authors wish to change the name from choroideremia to progressive choroidal atrophy. A large number of families have been studied in the United States and Canada of recent years, and this important disease has aroused considerably more interest than has retinitis pigmentosa, which is known to be hereditary.

The volume of literature on diseases of the uveal tract has been adequately covered by Hogan (107) and Calhoun (108).

The most interesting inflammatory disease of the uveal tract studied in recent years is toxoplasmosis. In the past it was believed that this interesting chorio-retinal lesion occurred only "in utero" but the findings of Hogan, Thygeson & Kimura (109) have changed this view. Busacca and associates (110), Wegmann & Gut (111) and Koke (112) have confirmed that toxoplasmosis may produce a chorioretinopathy in the adult. While the toxoplasmic antigen and complement-fixation tests are not entirely accurate, the methylene blue dye test is the most reliable test for toxoplasmosis Busacca and associates (110) reported 28 5 per cent positive results in adult patients with active chorioretinitis, whereas, when the same test was performed on controlled patients without chorioretinitis, he found only 3 per cent positives At the recent meeting of the Association for Research in Ophthalmology in San Francisco, considerable more evidence was presented to indicate that adult infection does occur

Sympathetic ophthalmia.—Evidences to support the two theories of sympathetic ophthalmia are still being presented Collins (113) has continued his work, using adjuvants combined with uveal pigment The adjuvants were aquaphor, liquid petrolatum, and heat-killed tubercle bacilli. This work would suggest that sympathetic ophthalmia is due to a bacterial hypersensitivity or a sensitivity to uveal pigment in which bacterial substances act as the adjuvant.

Schreck (114), however, believes that the chicken represents a natural reservoir for a virus which is the cause of sympathetic ophthalmia. Schreck's work has been substantiated by Redslob (115). They claim that this ultra-

of control at which the disease has been maintained. Hypertensive retinopathy and other diseases of the retina are reviewed extensively in the references given.

Detachment of the Retina

The prognosis regarding detachment of the retina following surgical therapy has improved so much of recent years that it is worthy of mention. The symposium on retinal detachment at the American Academy of Ophthalmology and Otolaryngology gives a concise and uniform opinion of the present day information on this important ocular disease (125). Surgical diathermy in the region of the break in the retina appears to be the best form of treatment. Pischel (126) and others (127) emphasize the importance of localization and accurately closing the break in the retina at the time of surgery. The prognosis of retinal detachments has improved since the importance of careful surgery and surgical treatment was stressed by Arruga (127)

NEUROMUSCULAR OPHTHALMOLOGY

The association of the extra-ocular muscles and binocular vision is of enormous interest to all ophthalmologists The symposium on strabismus published in 1953 expresses the combined opinion of six leaders in this specialized field (128). All parts of the world are beginning to show a considerable agreement on the best methods of treatment of strabismus. In spite of a close agreement on treatment, very little is understood regarding its basic etiology.

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the dosage of Diamox. While there is a great deal of variation in the method of administration, I give an initial dose of 500 to 1000 mg. This is followed by 125 to 250 mg. every 4 hr. for the first 24 hr. Then the dosage of Diamox is decreased as indicated.

DISEASES OF THE RETINA AND OPTIC NERVE

Maumenee (119) and Wagener (120) have reviewed the recent literature on diseases of the optic nerve in a complete fashion.

Of recent years retrolental fibroplasia has held the spotlight in ophthalmology. Since its original description by Terry (119) in 1942, a volume of literature has accumulated on this important disease. The disease is usually not present at birth but develops a short time after birth. The single most important factor was expressed by Duggart (121). He states that, "The incidence of retrolental fibroplasia is inversely proportional to the birthweight" One out of seven premature babies with a birth weight of 3 lb or less will have retrolental fibroplasia. One out of 16 with a birth weight of 4½ lb. or less will have the disease In spite of the volume of literature, the etiology, except for prematurity, is not known. Many authors have incriminated oxygen concentrations as a factor More research will be necessary before the final decision can be made.

Of recent years ophthalmologists have made fundamental contributions to the pathological nature of the vascular degenerative lesions of diabetes. The method of injecting the entire retinal vascular tree with special stains has contributed significantly to our knowledge. The majority of patients with diabetic retinopathy, and particularly those with micro-aneurysms, have been shown to have Kimmelstiel-Wilson's disease of the kidney at autopsy. There is a marked similarity between the capillary aneurysmal dilatations of the retinal vessels and the changes that occur in the glomeruli of the kidney. In the past few years, Becker (122) and Friedenwald (123) have made important contributions to the understanding of the vascular degenerative lesion. They noted that diabetic patients during pregnancy, in the absence of hypertension, developed retinopathy which usually disappeared after delivery. This suggested an endogenous increase in the adrenocorticotropic hormone. Becker (122), therefore, made rabbits diabetic with alloxan and gave them injections of corticotropin. An ophthalmoscopic picture resembling early diabetic retinopathy was found in these animals Examination of flat preparations of the retina revealed many capillary aneurysms. From these studies it would seem that the corticotropins have some part to play in the development of the retinopathy of diabetes

The argument concerning the control of diabetics still continues but it is the opinion of Wagener (120) that the absolute management of the diabetic probably will prevent retinopathy Although some authors, such as Cordes (124), state that the young diabetic who survives 20 yr is likely to have a severe form of diabetic retinopathy with loss of vision, regardless of the level

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PEDIATRICS[1,2,3]

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Introduction

In covering subject matter as broad as that of Pediatrics, it is far from easy to give full credit to current advances in so diverse a field, and it is difficult, if not impossible, to recognize contributions which by further developments or more conclusive investigations, will be revealed ultimately as of unusual significance. The task was undertaken realizing full well that the material selected and the opinions expressed will not be considered authoritative Choice of subject, therefore, has been determined by the interests of the authors and their departmental associates, and has been influenced by medical confreres. While much will have been omitted, what has been included has seemed of particular interest to the group

Problems of the Newborn Infant

During the neonatal period many physiologic adjustments are required of the newborn infant. A better basic understanding of the attendant problems has led to more intelligent care of well infants, and to more satisfactory diagnosis and treatment of those showing signs of disease.

Retrolental Fibroplasia.—This condition, more descriptively termed retinopathy of premature infants, is directly related to the degree of prematurity. Prevention of this serious disease entity is of great importance, and within the past few years information concerning its etiology has been accumulating In a recent discussion of oxygenation in relation to retrolental fibroplasia, the condition was attributed to excessive oxygen supply to the premature infant in the neonatal period (1, 2) Other factors probably influencing the onset and severity of the disease have been suggested on the basis of careful studies: excessive warmth and humidity, electrolyte shifts, and enzyme derangements In one group studied, premature infants, four pounds or under, were placed alternately in high and low oxygen concentration Of 36 infants in the high oxygen group 22 (or 61 per cent) showed retinal vascular change, and eight (or 22 per cent) irreversible cicatricial retinopathy. Of 28 comparable infants in the low oxygen group only two (or seven per cent) showed vascular changes, and neither developed per-

[1] The survey of literature pertaining to this review was completed in July, 1954

[2] The following abbreviations were used in this chapter ACTH (corticotropin), PAS (para-aminosalicyclic acid); AHG (antihemophilic globulin), PTC (plasma thromboplastin component), PTA (plasma thromboplastin antecedent)

[3] The authors take pleasure in acknowledging the invaluable suggestions of the pediatric departmental members, more particularly, C W Daeschner, M. M Desmond, H. K, Hsu, D. G McNamara, F M Taylor, and A P Williamson

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infant is well recognized, their use under individual circumstances to be evaluated largely by the pediatrician in charge.

Erythroblastosis Fetalis Attributable to ABO-Incompatibility—Jaundice appearing in an infant during the first 24 hr. of life can almost invariably be accounted for on the basis of erythroblastosis fetalis. While much has been written concerning this general subject, erythroblastosis as a result of incompatibilities in the ABO-series is not yet completely understood. The relative importance of ABO-incompatibility in the production of erythroblastosis is indicated in a recent survey of 2624 births, showing 14 instances of Rh incompatibility and 19 instances of ABO incompatibility (8). For all practical purposes, the diagnosis of ABO-erythroblastosis can be made, in the absence of manifest infection, if there is a major blood group difference between the mother and infant, by a negative Coombs test, by evidence of clinical jaundice in the first 24 hr. of life, and by a serum bilirubin level of more than 10 mg per 100 cc. The disease affects first-born infants with about the same frequency as those in later position in the sibship. At the present time the criteria for therapy in ABO-erythroblastosis are the same as those recognized for difficulties attributable to Rh incompatibilities.

Neonatal Tetany—Hypocalcemic tetany in two prematurely-born siblings has been reported recently which was associated with hyperparathyroidism in the mother (9). Clinical manifestations of tetany which were unusually severe and persistent in these two infants led to the discovery of hyperparathyroidism in the mother. In the first child tetany persisted through the twenty-first day of life, antitetanic therapy could be terminated on the twenty-sixth day, and the patient was discharged in good general condition with no evidence of further difficulty. In the second child convulsions persisted steadily for the first 11 days of life By the twenty-seventh day all antitetanic therapy could be discontinued, and the child remained in good condition. On the basis of these observations in the children, the mother was subjected to careful medical investigation Subsequently a parathyroid adenoma was removed surgically with favorable results.

Postmaturity—An infant delivered after a gestational period of more than 300 days is considered postmature by the majority of physicians. Postmaturity, the incidence of which is approximately 5 per cent, or one in 20 pregnancies, ranks second only to prematurity as a cause of fetal and neonatal mortality. Among 2178 women included in a statistical study, prematurity accounted for 36 per cent of the perinatal deaths and postmaturity for 30 per cent where the incidence of neonatal death was approximately 15 per cent (10) Postmaturity seems to be a hazard unique to primigravida, and it has been stated, on the basis of available records, that 73 per cent of primigravida, whose period of gestation lasted 300 days or longer, did not become pregnant again during the following 10 years

The clinical findings of the postmature syndrome may be divided into three general groups, depending upon the degree of placental dysfunction

manent damage. From such studies, retrolental fibroplasia would seem to be related significantly to excessive oxygen administration, with the general conclusion that its control may be possible by "severely limiting oxygen administration in premature infants" (2). Pertinent statistics presented at the May, 1954 meeting of the American Pediatric Society indicated that the prevalence of premature retinopathy is two to three times as great in large well-staffed hospitals where oxygen is more readily available for routine use (3). If, as has been suggested, the fetus is accustomed gradually during pregnancy to a decreasing oxygen supply, the unphysiologic fluctuations in oxygen levels to which the prematurely-born infant is subjected might well have a deleterious effect.

In one study the pattern of growth and development of the eye was followed in a large series of small, premature infants, 320 over the period from April, 1950 to January, 1953 (4) The fundi were classified as immature, transitional, and mature. Of the 320 premature infants followed, 86 developed retinopathy, of whom 38 had massive retinal edema with detached retina and malignant hemorrhages. From this study the general conclusion was drawn that there are critical periods of development in the eye when various factors might allow retrolental fibroplasia to occur, and that the immature eye of the small premature is undergoing a critical period of differentiation in an extra-uterine environment.

Further investigation is necessary for an evaluation of the various points of view with respect to retinopathy of the premature infant. As the result of a recent study in Scandinavia the recommendation was made that oxygen be resorted to only in pronounced asphyxia, and only under close supervision, and that withdrawal from oxygen should be gradual in order to avoid sudden changes in tension (5).

Water Loss in the Newborn Infant.—Controlled studies concerned with the effects of supersaturated atmospheres (mists) upon the economy of body water in newborn infants have indicated that such supersaturation of the atmosphere reduces insensible water loss, particularly that from the lungs (6, 7). The minimum daily water loss from the lungs in resting newborn infants was calculated to be from 6.4 to 12 3 gm per kg. of body weight with an average loss of 8 6 gm. per kg Insensible water loss from the body surface was unaffected by mist, whereas that from the lungs was reduced by about 80 per cent Solutions containing spreading agents as a source of mist did not seem to enhance the effect of the vapor

Physiologic hemoconcentration occurring normally in infants without oral intake for the first 70 hr of life was not noted in those kept in mist While hemoconcentration in normal infants has not seemed to be attended by obvious physical signs, its avoidance by the use of mist is of clinical interest, particularly as applied to very small or sick infants where danger of aspiration makes feeding extremely difficult for the first few days of life. The value of mists in the treatment of respiratory disorders of the newborn

The well-known congenital defects of the heart and other parts of the vascular system, digestive tract, as well as the numerous developmental arrests in various parts of the body, remind the observer of the great loss in ability that the race suffers as a result of faulty development. These defects in construction must be considered a disease which causes death of about 23 per cent of the human race before or shortly after the time of birth, and handicaps a certain proportion of the survivors throughout their lives. We carefully study and use all known precautions to protect ourselves against postnatal infections and diseases, and much interest and time is given to combatting the causes, yet little is said and scarcely anything done towards control of development or the hygienic protection of the developing individual.

The magnitude of this problem of congenital malformations and birth injuries in surviving newborn infants is reflected by statistical studies undertaken in some of the larger cities which have indicated an over-all incidence of 9 to 10 per thousand live births for congenital defects and 2 to 3 per thousand for birth injuries (13) The social, economic, and medical aspects of the care of this large group of defective children emphasize the importance of continued research into the causes and possible prevention

The rubella problem and the possible role of other infectious diseases in the mother, especially during the first trimester of pregnancy, have received considerable attention in recent years (14). In the case of rubella, surveys in Australia indicated an incidence of four abnormal to one normal child, if the disease occurred in the first trimester of pregnancy. Incidence in the United States based on pooled statistical studies seems to be of the order of 17 per cent; statistics in the British Isles show a comparable incidence It is of interest from the standpoint of susceptibility to viral infections that an increased incidence of rubella itself has been reported for pregnant women in the first trimester over that observed in later stages of pregnancy Evidence is accumulating that the fetus may suffer damage from a virus infection in the mother which clinically passes completely unnoticed It is well known that symptoms of rubella may be mild and variable; cases of rubella without skin manifestation have been reported, and such persons are capable of transferring the disease to other susceptible individuals (15). Material for study of the micropathology of congenital defects in human subjects is not abundant. A few such studies, however, have been possible; detailed pathologic findings were recorded in several cases of congenital deafness attributable to rubella. The malformation is thought to be of the sacculocochlear type, consisting of marked changes in the stria vascularis with resultant collapse of the cochlear duct and sacculus, incomplete development of the tectorial membrane and of the organ of Corti. In pathogenesis this defect resembles an hereditary defect seen in certain varieties of dogs (16)

The possibility of fetal damage by virus infection which gives mild or no clinical manifestations in the mother has been discussed in connection with other virus diseases. A previous review by Schick emphasized the danger to the fetus when immune or partially immune mothers are exposed to variola. Varicella was reported recently in newborn twin infants whose mother ex-

In the first stage, the infant's skin shows the effects of loss of vernix, is dry, cracked, parchment-like, or peeling, but is not stained by meconium The infant may appear malnourished, or even emaciated, with an old or worried look, reflecting failure of the placenta to provide proper nutrition. However, in this stage the infant is usually open-eyed and alert and as a rule survives The second stage of the postmaturity syndrome shows the effects of more extensive placental degeneration, function in this stage being reduced to the point of producing fetal distress attributable to anoxia, with the liberation of large quantities of meconium into the amniotic fluid The amniotic fluid, the infant's skin, the umbilical cord, and the placental membranes are meconium stained. About one-third of these postmature infants die. In the third stage of postmaturity, the infant is assumed to have passed through the first two stages in utero and to have experienced intra-uterine anoxia for days, or perhaps weeks, before birth. The majority of these infants die in utero. In babies who are live-born at this stage the green bile staining of the meconium has changed to a yellow discoloration The infant's nails and skin are stained a bright yellow, and the cord shows a dirty yellow, or yellowish-green color. About 15 per cent of these third-stage babies die within a few hours to a few days following birth. One such infant who succumbed one hour after delivery showed signs of meconium pneumonitis. Autopsy findings in another who died at eight days of age, revealed bilateral patchy atelectasis and marked emphysema As a rule, the various degrees and stages of placental dysfunction are readily recognizable by the clinical findings in the infant at birth

The problem of postmaturity has been emphasized also by recent physiologic studies during gestation which indicate that the supply of oxygen in a clinically normal pregnancy falls gradually up to the 40th week, and declines rapidly thereafter (11). In consequence, all fetuses have a low oxygen supply and practically no reserve by the forty-third week. Fetuses with a supply already deficient are likely to experience oxygen deficiency during labor In a review of 11,051 deliveries covering the period from 1948 to 1952, it was apparent that obstetric death was three times as high at 43 weeks as at 40 weeks, and that increase in stillbirths accounts for this difference In many of these, exact assignment as to the cause was not possible except to a general category of fetal distress. The hazards of postmaturity include not only risk of fetal loss, but serious damage to surviving infants with possible untoward sequelae.

CONGENITAL MALFORMATIONS

Biologists and clinicians alike have recognized for many years that two main mechanisms are involved in abnormal development intrinsic abnormalities of germinal origin and those abnormalities which are produced by external influences upon essentially normal ova As early as 1909 the following commentary appeared in the literature (12).

(24). Fetal loss from resorption and abortion was as high as 90 per cent in treated animals

The teratogenic potentiality of ionizing radiation in experimental animals has been verified by recent investigations (25, 26, 27). Incidence of specific abnormality was high when exposure occurred during periods of major organogenesis Primitive differentiating cells of the mammalian nervous system seem particularly vulnerable. In some stages of embryonic development a certain amount of damage repair was possible, provided total radiation dose was not too great

Possible damage to the fetus by hormone therapy in the mother, especially early in pregnancy, has been considered and some evidence has been recorded: three possible clinical instances, and in studies on experimental animals (28, 29) Likewise, the effects of unusual environmental factors such as high-altitude hypoxia are under discussion as possible sources of fetal damage In some areas the occurrence of certain cardiovascular anomalies, including patent ductus arteriosus and persistent interatrial communications, is thought to be correlated statistically with high-altitude environment of the mother during pregnancy (30).

That the importance of this problem of fetal damage and the subsequent care of defective children is becoming more apparent is evidenced by the extensive investigative studies in progress in this field

Toxoplasmosis

Toxoplasma gondii, identified as early as 1908, is considered an obligate intracellular protozoan, the exact classification of which is still in question. In smears it appears as a crescent-shaped organism, about 3 by 5 microns in size, showing a small, centrally located, chromatin body In fixed histologic sections the parasite appears smaller, more round in contour, and in addition to single forms, cyst-like aggregates are seen suggesting intracellular multiplication Various species of animals and birds in nature are believed to be infected. pigeons, rats, mice, rabbits, sheep, cats, and dogs

Toxoplasmosis as a human infection was first recognized in 1939 with the isolation of *Toxoplasma gondii* from infants showing a granulomatous encephalomyelitis, the agent being established in laboratory rabbits and mice About the same time human strains and naturally-occurring animal strains were shown to be identical morphologically, biologically, and immunologically. Human infection is wide-spread geographically as shown by case incidence and by antibody studies North, Central, and South America, Europe, Australia While transmission by vector is a possibility, isolation of the organism from the excreta of infected animals and birds suggests transfer to man by direct contact or contamination of food

Human toxoplasmosis may be manifested in a number of ways a fetal or congenital form in which encephalomyelitis and chorioretinitis are prominent features with organisms demonstrated in both brain and ocular lesions; an acute encephalitis in children, a short febrile illness in adults character-

perienced a mild varicelliform type of rash the day before delivery (17). Likewise, western equine encephalomyelitis was identified as the cause of illness in twins; the mother recalled in retrospect having received numerous mosquito bites about ten days previous to delivery, as well as suffering from severe headache and malaise two to three days before delivery (18) In this particular case, however, preeclampsia may have been responsible for passage of the disease to the twin fetuses. Little is known concerning the mechanism of virus passage across placental barriers. Pertinent to this subject was a recent discussion of viremia in clinical variola and observations on the congenitally acquired disease, which suggest that infection of the fetus in utero through the placental circulation occurs at about the time of onset of illness in the mother (19). In those instances in which illness began in the mother before delivery, eruption occurred in the infant within ten days after birth.

The question as to whether vaccination for smallpox is advisable early in pregnancy has been the subject of recent comment, a case of severe congenital generalized vaccinia having been reported in a hydropic premature infant whose mother experienced a marked primary reaction to vaccination toward the close of the first trimester of pregnancy (20). Statistics collected in the area of this observation showed that among 34 women vaccinated between the fourth and twelfth weeks of pregnancy there were 10 abortions, 5 stillbirths, and one congenital abnormality However, in connection with the vaccination of an estimated 80 per cent of the citizens of New York City during 1947, no increased incidence was observed in congenital malformations, still births, or infant deaths among the vaccinated women (21). In experimental studies being carried out in swine, vaccination of pregnant sows with attenuated hog cholera virus resulted in miscarriages, stillbirths, and malformations without producing detectable signs of illness in the sow (22)

Virus disease in the mother, whether subclinical or definitely manifest, is unpredictable in its effect upon the fetus, incidence of damage to the fetus is variable, and the possible factors which might permit or enhance damage to the offspring are not understood Attempts to approach this problem experimentally are in progress; for example, the experimental production of developmental defects in the chick by exposing the embryo at various stages to Newcastle disease virus, an infectious agent to which chickens are susceptible (23) A high percentage of gross defects may result, depending upon the concentration of virus suspension used, the degree of direct accessibility of susceptible structures to the virus, and the stage of development of the embryo at the time of infection

Nutritional disturbances, deficiencies, or imbalance, as possible sources of teratism, have been investigated extensively at recent years in experimental animals. A mild hypervitaminosis A in rats, especially early in gestation, has been shown to give rise to congenital anomalies exencephaly, cleft palate, macroglossia, shortened mandible and maxilla, and gross eye defects

Heart Disease in Children

Emphasis continues to be placed on the diagnosis and treatment of heart disease in infants and children, stimulated by the development of improved diagnostic methods and more effective therapeutic measures, and by the phenomenal advances made in the treatment of patients with cardiac conditions amenable to surgery.

Detailed study of many children with signs and symptoms of heart involvement has revealed that in addition to rheumatic and congenital heart disease, which constitute the two most important cardiac categories in the pediatric age group, a small but very interesting group has been recognized which is designated as primary myocardial disease (42) These patients have certain findings in common cardiomegaly, absence of murmurs, electrocardiographic abnormalities, and normal blood pressure. In careful studies reported recently on 45 such patients, all infants and children, the heart showed characteristic enlargement on roentgenographic examination, with globular silhouette and often with evidence of left ventricular hypertrophy. Electrocardiograms indicated myocardial damage. In congestive failure which occurred in many of these patients, response to digitalis therapy was remarkably favorable. *It was striking that this group of patients with primary myocardial disease showed unusual sensitivity to digitalis not only with respect to clinical response but also in the development of toxic signs attributable to the drug.*

In 26 of these patients who came to autopsy, the following pathologic processes were observed: glycogen storage disease of the heart (3 patients); aberrant left coronary artery (1 patient), medial necrosis of coronary arteries (2 patients); idiopathic myocarditis (10 patients); and subendocardial sclerosis (10 patients). Ante mortem differentiation of the particular process accounting for individual clinical manifestations proved difficult. However, certain features characterizing each type of primary myocarditis were considered helpful in differential diagnosis Distinguishing features of glycogen-storage disease with heart involvement included age of symptoms between two and six months, never beyond 18 months; history of a similar disorder in a sibling, absence of congestive failure in the presence of marked cardiomegaly; and skeletal muscle biopsy showing high glycogen content. Aberrant left coronary artery as a cause of primary myocarditis was suggested by onset between the ages of two and six months, tachycardia, respiratory distress, cyanosis, and profuse perspiration during "attacks," especially with feedings, often symptom free between "attacks", absence of congestive failure, and x-ray evidence of bulging prominence in the region of the left ventricle Medial necrosis of coronary arteries was suspected in patients who presented evidence of systemic disease especially involving the kidneys, with onset at less than three months of age, associated congenital abnormalities and absence of congestive failure. In idiopathic myocarditis, first reported in a child as early as 1901, salient features included age of onset beyond six months, likelihood of this form of heart disease increasing markedly with onset beyond one year of age, presence of abnormal heart sounds;

ized by an atypical pneumonia and a maculopapular rash which clinically may simulate diseases of the spotted fever group; and a latent infection, usually asymptomatic. A glandular form has been described with recovery of the organism from an excised axillary gland (31). Recently attention has been drawn to the association between a *febrile illness in children, an outstanding feature of which was lymphadenopathy*, and positive serologic tests for toxoplasmosis (32). These children were seen commonly in the out-*patient department* suffering from unexplained fever and generalized lymphadenitis, accompanied in some instances by a rash and splenomegaly. Laboratory findings included significant leukocytosis with increased polymorphonuclears, and negative Paul-Bunnell tests. One such child of five years showed marked rise in titer of antibody to toxoplasma, and from his *blood and saliva* toxoplasma organisms were isolated by animal and embryonated egg inoculation. French workers have described a similar entity with recovery of toxoplasma from throat smears, and suggest possible entry by bucco-pharyngeal route (33).

Specific tests of diagnostic value include neutralization skin test on rabbits, *complement fixation antibody detection, and the dye or slide* neutralization test (34) Neutralizing antibodies appear early in acute toxoplasmosis and may persist for years; complement-fixing antibodies appear somewhat later and decline more rapidly. Laboratory methods of isolation include intraperitoneal inoculation of mice and guinea pigs, rabbit-skin inoculation, use of the embryonated egg and, more recently, of tissue culture (35, 36, 37). An antigen, toxoplasmin, derived from mouse peritoneal fluid or egg fluid, is available for skin testing

No satisfactory treatment for toxoplasmosis has been developed In general antibiotics have not proved effective. Therapy with sulfonamides, promising in early experimental studies in mice, failed to eradicate infection,
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drugs, particularly diaminopyrimidines, such as Daraprim (5-p-chlorophenyl-2,4-diamino-6-ethyl pyrimidine), and the sulfonamides in combination have been employed experimentally with some success. Extensive therapeutic studies of experimental toxoplasmosis in mice have shown the combination of Daraprim and sulfadiazine superior to either drug alone Clinical application in human infection has not been evaluated (38).

Prognosis in congenital toxoplasmosis is uniformly poor. In a recent analysis of more than 100 cases sequelae were listed in order of incidence: chorioretinitis, cerebral calcification, psychomotor retardation, hydrocephaly or microcephaly, and convulsive disorders (39, 40) In this series of patients, *mothers were followed, wherever possible, for subsequent pregnancies*, and none of 35 children born subsequently to mothers of patients with congenital toxoplasmosis was abnormal Prevention by treatment of the expectant mother is considered a possibility. Obstetricians are becoming aware of the methods available for early detection of sero-positive [illegible]

the role of the domestic cat in its transmission seems to have been established (48). Recognized as early as 1930 by French physicians and by several observers in the United States, the disease as an entity has been brought to general attention comparatively recently. The nomenclature has included cat scratch or cat bite fever, cat-claw disease, and benign inoculation lymphoreticulosis. While the etiologic agent has not been identified exactly, it is thought to be a virus of the psittacosis lymphogranuloma venereum group. Attempts to isolate bacterial and mycotic agents from suppurative lymph node material have been consistently unsuccessful Transfer of the disease to monkeys and to human volunteers has been accomplished. Stained sections of primary skin lesions and involved lymph nodes from both man and monkeys show large numbers of intracellular and extracellular granule-like bodies similar in appearance to the elementary bodies characteristic of psittacosis (49).

The disease is probably world-wide in distribution, cases having been reported from Great Britain, United States, India, Japan, Switzerland, and France. Antigenic skin-test studies performed cooperatively indicate that the disease is very similar or identical in this country, in Britain, and parts of Europe. On the basis of similarity in the type of elementary body, possible relationship between the etiologic agent of cat scratch fever and that of feline pneumonitis has been suggested. The infectious agent responsible for the latter is related antigenically to the psittacosis lymphogranuloma viruses. However, cats as a rule show no evidence of illness associated with their ability to transfer the agent to human subjects and have no reaction to the intradermal injection of its antigen, so that their role is considered a passive one. Other means of transfer have been recorded, by scratches from thorns, pasture fences, infection of minor abrasions on the hands of abattoir workers, suggesting that the agent may be widespread in animal and possibly in vegetable life.

Examination of involved lymph nodes has revealed only nonspecific morphologic changes which have been classified into distinct phases: (*a*) an "elementary" phase of simple hyperplasia, (*b*) an "accentuated" phase in which, in addition to hyperplasia, areas of early cellular necrosis stain as acidophilic masses; and (*c*) the "ultimate" stage in which the lymph node architecture is displaced by multiple areas with central necrosis and by circumscribed foci of epithelioid cells and scattered giant cells of the Langhans type (pseudotubercles) The final stage corresponds to the clinical stage when the enlarged node becomes fluctuant (50)

While clinical manifestations may vary considerably, as a rule, the presenting picture is one of malaise, low grade fever, and unexplained local adenopathy The patient may not appear acutely or chronically ill; however, the size of the involved lymph node, or nodes, is often striking. The history in most instances will reveal association with cats, with or without the recollection of a specific abrasion. The incubation period is variable, being from 10 to 30 days from the date of probable inoculation In one volunteer subject minimal regional adenopathy began in about eight days; the nodes enlarged

evidence of congestive cardiac failure with good response to digitalis therapy. The clinical manifestations of subendocardial sclerosis were considered so similar to those of idiopathic myocarditis as to be indistinguishable.

The possible use of steroid therapy in rheumatic fever and rheumatic carditis has been the subject of considerable discussion in recent months The response of patients with rheumatic fever to steroid therapy has been difficult to evaluate since the natural history of this disease is so variable and the severity of any single attack is usually impossible to predict. In some cases favorable response to the administration of steroids early in the patient's clinical course, or in first attack of carditis, has suggested that the course of active carditis might be altered by decreasing both the severity and duration of the attack, and that in reducing the severity of acute exacerbations, steroids might also be useful even in patients with chronic rheumatic carditis (43, 44, 45). This important subject is, however, still controversial. The problem is expressed in concise terms in recent editorial comments:

> We do not believe that at present it (steroid therapy) should be used except in hospitals where the patients can be closely observed, studied, and followed with the purpose of throwing further light on its value, or lack of value in preventing permanent cardiac damage (46).

Stress continues to be placed on prevention of rheumatic fever, and various therapeutic regimens have been employed The three antibiotics, penicillin, *chlortetracycline (aureomycin), and oxytetracycline (terramycin)*, seem to be equally effective in controlling the symptoms and signs of acute streptococcal tonsillitis and pharyngitis However, the effect of antibiotics on acute rheumatic fever and acute glomerulonephritis remains to be determined In a controlled series of 2044 patients with exudative tonsillitis, or pharyngitis, chlortetracycline therapy rapidly reduced the incidence of hemolytic streptococcus carrier state, and antibody production decreased as ... over a

Evidence has been accumulating which indicates that eradication of the infecting organism, especially group A streptococci, is of great importance if rheumatic fever is to be prevented Treatment of streptococcal sore throat should be initiated as early as possible after the onset of illness

... hours apart ... hose indi- ... t in doses ... be employed, because ... dule of treat-

Infectious Disease in Children

Cat Scratch Fever (Benign Inoculation Lymphoreticulosis).—Cat scratch fever has come to be recognized as a relatively common disease of man, and

some cases, fibrosis has resulted in persistent enlargement. No specific therapeutic measures are known to be of definite benefit. Chlortetracycline has appeared to shorten the febrile course in some instances; in others the regression of nodes has seemed more rapid during therapy with either oxytetracycline or chloroamphenicol. Further experience is needed for evaluation of their therapeutic effectiveness. Occasional drainage by aspiration will hasten resolution of fluctuant nodes, but this procedure carries the risk of a draining sinus; these apparently heal in time leaving a minor scar.

Infectious Mononucleosis.—Infectious mononucleosis is a common disease (55), occurring in epidemics in children between the ages of two and ten years, with a peak incidence among children five to six years of age. Rare in infants under six months, it has been recorded in epidemic form in children from the ages of six months to two years. The common occurrence and protean manifestations of this disease make it a diagnostic possibility to be considered in all conditions presenting themselves as throat infections, colds, influenza-like disease, and the common contagious diseases. The incubation period is considered to be about 11 days Consistent clinical manifestations are marked malaise, sore throat, and fever, which may continue for a matter of weeks. Enlargement of lymph nodes, which may become apparent very early or later in the clinical course, is marked and usually occurs in characteristic sequence. Splenomegaly is common and may persist for months. Skin rashes have been observed which simulate the common exanthemata. Essential laboratory findings are the characteristic changes in the monocytes in the peripheral blood and a positive heterophile antibody test. The latter usually becomes positive during the first week following onset, and remains positive for a varying period of time In some instances the rise of agglutinins is slow, giving an initial negative reaction. Modifications of the Paul-Bunnell heterophile test have increased its specificity as a diagnostic test. False positive Wassermann reactions may be obtained in this disease The infectious agent is generally considered to be viral in nature; blood from patients in the acute phase has produced similar disease when injected into monkeys and rabbits (56, 57).

Therapy is supportive and nonspecific, the effectiveness of antibiotics being still in question (58). Prognosis, in general, is good, even in the prolonged or more severe cases. The convalescent period, however, is usually prolonged, especially in adults, weakness and easy fatigability may persist. Fatalities have occurred as a result of ruptured spleen. Recent reports have emphasized the more serious manifestations, complications, and possible sequelae (55, 59 to 67) These have included extensive liver involvement confusing the diagnosis with that of infectious hepatitis, acute pericarditis and involvement of the heart; hemolytic anemia, severe central nervous system involvement, with coma, and personality changes, which was, in one instance, followed by a temporary convulsive disorder; pleural effusion with possible infiltration of the pleura by mononuclear cells and lymphocytes, follicular conjunctivitis with periorbital edema, and, in some instances,

progressively, becoming fluctuant in about 20 days. At the height of the lymph node response a skin papule appeared at the site of the primary intradermal inoculation and persisted for several days.

The foregoing sequence observed in a human subject infected experimentally appears to be characteristic of the patient infected naturally; at the time that medical advice is sought there is usually an exacerbation of redness and swelling at the site where a primary lesion is in the process of healing. This lesion tends to heal slowly, and may resemble an insect bite, a small furuncle, or a scab following simple trauma. The nodes are those which drain the area where the initial lesion occurred, commonly the epitrochlear, axillary, submandibular, cervical, or inguinal ones The skin overlying enlarged nodes may show some redness, but more often it is normal in appearance. Individual lymph nodes may be hard or soft and vary in diameter from 1 to 5 cm.; on aspiration a purulent fluid may be obtained from which no bacteria can be cultured. Unusual clinical manifestations have included cervical adenitis, thought to be attributable to inhalation or aspiration of the etiologic agent; a cervical form with negative cervical nodes, but having a nontender mass in the suprasternal notch; transient pulmonary infiltration in patients with a history of cat scratch who showed typical clinical manifestations of cat scratch fever; an oculoglandular form of the disease associated with conjunctivitis (Parinaud's conjunctivitis), and cervical adenopathy (51) Central nervous system manifestations have been recorded, and may be severe, lasting in one instance for about four days, with coma for a period of 48 hr. (52, 53). One child in whom a diagnosis of cat scratch fever was made had an osseous lesion (ilium) in addition to cervical lymphadenopathy. Histologic changes in the excised node and in the soft tissues adjacent to the involved bone were comparable (54).

While the usual laboratory studies are nonrevealing, moderate leukocytosis with slight shift to the left has been observed. Agglutination tests for *Pasteurella tularensis*, *Brucella abortus* and *melitensis*, and the heterophile antibody test for infectious mononucleosis are consistently negative Though some patients may show a low titer of antibody to lygranum antigen by complement fixation test, the intradermal Frei test for lymphogranuloma (lygranum antigen) is negative Patients with cat scratch fever show consistently a positive skin reaction from the intradermal injection of the antigen prepared (Frei procedure) from pus obtained from an involved lymph node of a known case. However, the intensity of the skin reaction varies considerably in the individual case.

The cat scratch syndrome is most commonly confused with simple pyogenic adenitis, but must be differentiated also from tuberculous adenitis, tularemia, Hodgkin's disease, lymphoma, fungous infections, and lymphogranuloma venereum The characteristic lymphadenitis in some instances may be accompanied by erythema nodosum-like lesions on other areas of the body. Prognosis is uniformly good, the enlarged nodes regressing spontaneously in one to three months after reaching their peak enlargement. In

viral agent, ordinarily localized in certain tissues, becomes generalized. Similar cytopathogenic agents have been isolated from eruptive lesions in varicella and in herpes zoster, both have been propagated in human tissue culture and give rise to the same type of eosinophilic intranuclear inclusion body.

The virus of herpes simplex may produce serious, often fatal, generalized disease, especially in young children; necropsy studies have been reported with extensive findings in brain, liver, diaphragm, lungs, and with rounded necrotic foci in the mesentery (72) Virus has been recovered from tissues of the liver and other visceral organs by means of mouse or embryonated egg inoculation. Typical intranuclear inclusions are observed in the cells of necropsy specimens and of tissues from the inoculated animals

Pertussis—Although vaccines for the prevention of whooping cough have been used for many years there is no suitable standard of potency for these vaccines (73). Stimson has estimated that only about 85 per cent of those injected with vaccine experience complete protection (74). The first standard of required potency for pertussis vaccine became effective January 31, 1949. A potency analysis of large numbers of pertussis vaccine aliquots demonstrated clearly the fallacy of dependence upon numbers of bacteria as a measure of the dose for human immunization purposes As a result, the method of estimating potency was changed from bacterial evaluation to an evaluation of the total human immunizing dose, irrespective of the number of bacteria per dose

The reference pertussis vaccine, Lot No 4, which had been used in the protection test of each lot of vaccine under consideration, was recently adopted as the United States standard. According to the best information available, the total dose of a vaccine equivalent in potency to that of 96,000 million bacteria of the standard would be adequate to afford significant protection to a child To this number of bacteria of the standard was assigned arbitrarily a value of 12 protective units (73)

In connection with this standardization, the mouse protection test was used as an index of potency, and the protective antigenic unit was developed. The potency of all newly-prepared whooping cough vaccines must be expressed in terms of antigenic units, the total dose of any preparation being 12 units In this manner pertussis vaccines can be standardized and their potency expressed regardless of the number of bacteria present in the preparation

Such standardization by protection tests should reduce the wide differences in immunity observed when vaccines are standardized on the basis of bacterial numbers, and probably by avoidance of excessive dosage, would reduce the incidence of reactions Since no specific chemotherapy or antibiotic preparation effective against *Hemophilus pertussis* has been forthcoming, active immunization against this disease is of great importance

Tuberculosis—In this field the past several years have been marked by concerted efforts to evaluate the therapeutic effects of various combinations of drugs (75, 76) Under the direction of the Public Health Service a co-opera-

severe optic neuritis. A recent report deals with a patient suffering from infectious mononucleosis who showed severe liver involvement, azotemia, thrombocytopenia, and toxic course, in whom striking improvement accompanied the use of ACTH. However, the routine use of ACTH or cortisone in uncomplicated cases of the disease is not recommended (68).

Cytomegalic Inclusion Disease (Salivary Gland Virus).—Inclusion disease of the parotid is very similar to salivary gland disease of animals. In several species of rodents the presence of greatly enlarged cells containing intranuclear, and, in some instances, intracytoplasmic inclusions is known to be associated with a transmissible, species-specific viral agent. Intranuclear inclusions resembling those described in the salivary glands of rodents have been observed in the salivary glands of 10 to 30 per cent of autopsies performed on infants and young children, irrespective of the cause of death. In recent years cytomegalic inclusion disease has been recognized as a clinical entity, seen predominantly in young infants, but encountered occasionally in older children and adults. It is a systemic disease characterized by the presence of inclusion bodies in enlarged cells of many viscera. Affected cells may be epithelial or mesenchymal; various organ systems may be involved It has been suggested that the clinical manifestations vary according to the organ system most extensively involved, implying for example that one form might be predominantly respiratory, another renal, adrenal, hepatobiliary, gastro-intestinal, hematologic, cerebral, etc.

The most constant clinical pattern associated with the disease occurs in the newborn period, and the manifestations observed are those of a blood dyscrasia, liver damage, or both (69). Hepatomegaly, splenomegaly, jaundice, anemia, thrombocytopenia, and purpura may be observed Heart and thymic involvement has been reported, cerebral calcification may be present, and there may be evidence of severe cerebral damage Conditions to be differentiated in diagnosis of the disease in infants include septicemia, erythroblastosis, congenital syphilis, and toxoplasmosis. In some instances the diagnosis has been established by demonstration of characteristic inclusion bodies in cells of urinary sediment In older children, manifestations vary widely, but in most instances the predominant symptoms are associated with interstitial pneumonitis or enterocolitis No effective therapy is known.

The infectious agent responsible for cytomegalic disease is considered to be a virus similar to that isolated from the salivary glands of animals However, transfer of the human disease agent to experimental animals has not been accomplished to date It is of considerable interest that the virus of mouse salivary gland disease has been grown successfully in mouse tissue culture (70)

The etiologic agents of two other virus diseases, varicella and herpes zoster, associated with identifiable inclusion bodies, have been cultivated by means of tissue culture Recently visceral involvement was reported in an interesting case of generalized herpes zoster (71), emphasizing the wide variation in clinical manifestation associated with any condition in which a

with pulmonary tuberculosis who had received no previous antimicrobial therapy were eligible for this second study.

Progress reports of this second planned investigation have appeared from time to time. The first series comprised a total of 335 patients Of these, 78 were treated with isoniazid, 3 mg. per kg. body weight, plus streptomycin; 64 with isoniazid, 3 mg. per kg body weight, plus PAS; 73 with isoniazid, 10 mg per kg. body weight, plus streptomycin; 63 with isoniazid, 10 mg. per kg., plus PAS; and 57 with isoniazid, 10 mg. per kg, plus streptomycin, plus PAS Careful bacteriologic smear studies on sputum specimens indicated definite decline in percentage positive for all regimens, from a range of 71 to 89 per cent positive at the beginning of the study to one of 9 to 21 per cent positive at the end of the twentieth week. *No significant differences were observed* among the five regimen groups, the decline in positive specimens being about comparable

Objective changes in the chest x-rays were of interest in that the proportion of patients showing moderate or marked roentgenographic improvement increased steadily on all regimens throughout the 20-week period, by the end of which 62 to 68 per cent of the patients showed significant roentgenographic improvement Thus, also on the basis of chest findings, all five therapeutic regimens appeared to be effective in bringing about improvement

Toxic manifestations to isoniazid were noted in nine patients, all receiving 10 mg of the drug per kg of body weight Symptoms of peripheral neuritis appeared between the forty-second and ninety-fifth days of treatment, or, on the average, at about 65 days Among the nine, three were able to continue as planned; in two, it was necessary to reduce the dosage, and in four, isoniazid had to be discontinued entirely Subsequently all nine patients so affected by the drug improved and were completely free of toxic manifestations

The following trends seemed apparent from the co-operative studies (*a*) Isoniazid and PAS were as effective as isoniazid plus streptomycin, (*b*) all three antituberculosis drugs in combination were no more effective than either isoniazid and streptomycin, or isoniazid and PAS, (*c*) there has been no evidence thus far that the therapeutic effectiveness of isoniazid increases with increasing dosage Toxicity to isoniazid (isonicotinic acid hydrazide) was not observed, as a rule, in patients receiving 3 mg per kg, but among those receiving 10 mg per kg., about one in ten developed peripheral neuritis. In about one-third of those so affected, this manifestation was so severe as to preclude further use of isoniazid.

In addition to peripheral neuritis more severe toxic manifestations are being reported, and extensive studies are in progress in various laboratories which concern the effect of isoniazid on metabolic processes (77 to 80). Clinically the administration of vitamin-B complexes, particularly B_{12}, has seemed to reduce toxicity. Several other derivatives of isonicotinic acid have been investigated (isopropyl derivative, iproniazid, isoniazid Ro-2-4969, etc.), some of which have proved too toxic for general use.

tive investigation has been carried out, the purpose of which was a study of the efficacy of streptomycin para-aminosalicylic acid (PAS) and promizole® (a sulfone) in the treatment of miliary tuberculosis and tuberculous meningitis. A number of therapeutic schedules was employed in the treatment of 32 children with miliary tuberculosis, and 93 infants and children with tuberculous meningitis Follow-up studies on the 26 surviving children in the miliary group revealed that all 26 were alive on the last recorded date, two to four years from the first day of treatment, and showed no signs of miliary disease Of 24 patients who had been observed to be in good condition at the end of one year of treatment, 20 continued to do well. Four subsequently developed other types of tuberculosis: spinal, pulmonary, renal, and meningeal; but had no evidence of miliary involvement. Of the group with tuberculous meningitis, 42 patients (45 per cent) survived the first year, 24 with no serious sequelae. Follow-up studies of these survivors over a period of two to four years from initiation of chemotherapy revealed that 12 were living but had gross residuals, one patient could not be traced, and 26 were living without significant sequelae from the meningeal infection.

The addition of isoniazid (isonicotinic acid hydrazide) to the medical armamentarium against tuberculosis gave impetus to the cooperative studies. Physicians in 22 hospitals located in various sections of the country have been engaged in the most recent evaluation effort. The first report of the more recent studies was based on observations made on 1500 patients who were treated for 40 weeks on several therapeutic regimens. The results indicated that, under the controlled conditions obtaining, "isoniazid alone was approximately equal to streptomycin plus PAS,[2] while the combination of isoniazid plus streptomycin was slightly superior to both" (*75*). *Although* significantly fewer patients continued to produce sputum positive for tubercle bacilli, in those patients who did continue to produce positive sputum, the acid-fast organisms were almost invariably drug-resistant to streptomycin when streptomycin and PAS were administered, to isoniazid when this drug was the only therapeutic agent employed, and to both streptomycin and isoniaz [illegible]
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Hov [illegible] e
principal antituberculosis drugs, streptomycin, and isoniazid, prompted the *investigating groups* to study the effectiveness of isoniazid in combination with PAS, and that of a combination of all three, isoniazid, streptomycin, and PAS

Accordingly, the protocol for the second large-scale study, adopted in [illegible] Isoniazid (3 mg per kg.) plus strep- [illegible] S, (*c*) Isoniazid (10 mg. per kg.) [illegible] kg) plus PAS, and (*e*) Isoniazid (10 mg per kg) plus streptomycin and PAS

Streptomycin was given in dosages of 1 gm twice a week, PAS, 10 to 12 gm. *daily; and isoniazid in* doses of 3 or 10 mg. per kg. daily. Only patients

exposure to tuberculosis, admission of a child to a tuberculosis hospital should be discouraged until the diagnosis can be verified (84).

Hemophilia

Recent developments have shown that prolonged coagulation time may indicate deficiency in any of several substances necessary for thromboplastin activity (85 to 88). In consequence the concept of hemophilia as a readily definable clinical entity has undergone modification It has been suggested that hemorrhagic conditions of this type be classified tentatively as follows: (a) hemophilia A, defect in antihemophilic globulin (AHG), thromboplastinogen, plasma thromboplastin factor; (b) hemophilia B, defect in plasma thromboplastin component (PTC), called Christmas disease from the name of a patient, and (c) hemophilia C, defect in plasma thromboplastin antecedent (PTA) All three conditions are characterized by bleeding tendencies externally and into tissues, and in some cases by hemarthrosis following minimal or no trauma As a rule, coagulation time is prolonged while bleeding time and prothrombin time are within normal limits These disturbances cannot be differentiated solely by the character of the bleeding

Hemophilia A, classic hemophilia, is inherited as a sex-linked recessive. Typically clinical manifestations occur in the affected male progeny, and the trait is carried as an inapparent genetic character by the heterozygous female (carrier). Rarely, the condition may occur in females who are homozygous The true hemophiliac is unable to produce AHG[2] in adequate quantity Clinical manifestations may be evident in very early life as bleeding from cord or following circumcision, or the condition may not be apparent until the child is old enough to experience trauma, loss of teeth, etc Hemarthrosis with attendant sequelae is a characteristic finding, and may appear as soon as the infant begins to walk Bleeding in hemophilia may involve the viscera or the central nervous system Prothrombin time and bleeding time are normal while the thromboplastin generation test reveals a deficiency of antihemophilic globulin with inadequate activity of thromboplastin The diagnosis is verified by the so-called mixing tests, various combinations of fresh normal blood, or plasma, and known hemophilic blood, or plasma, as indicated

Families have been recorded in whom a mild form of true hemophilia occurred, apparently caused by partial lack of AHG In general, however, the hemophiliac lives in constant danger of serious disability or death Trauma is to be avoided so far as is possible, surgical procedures undertaken only under controlled circumstances Family adjustments are necessary

Fresh whole blood, or plasma, is essential in the treatment of acute hemorrhage. Since a small amount of AHG is usually sufficient, infusion of blood or plasma may be given slowly in order to allow time for effectiveness. If prepared and kept frozen under ideal conditions, fresh frozen plasma is effective, and may be kept for considerable periods An antihemophilic plasma is now available in dried form for use in travel, in emergencies in isolated areas, etc Preliminary accounts have appeared recently describing the use of bovine

The success of isoniazid therapy in the prevention of complications in primary tuberculosis in children, particularly meningitis, constitutes one of the major advances in the treatment of the disease (81, 82). In an attempt to initiate treatment as early as possible, immediate therapy with isoniazid alone, or in combination, has been recommended for recent tuberculin converters, whether children or adults, especially among those highly exposed.

The world-wide distribution of tuberculosis is well-known, and the problem is being emphasized in many areas (83). Primary tuberculosis among infants and children is under investigation in the vicinity of Nairobi, Africa, where presumably the population has not experienced exposure to the acid-fast bacillus and is relatively susceptible At the time of recent reports, 1149 children had been tested with intracutaneous tuberculin using 0.1 cc. of 1 to 1000 old tuberculin, and followed by 0.1 cc of 1:100 in negative reactors. In this series, 131 (or 1 per cent) were postive reactors. Thirty-one patients showed false negative tuberculin tests; all of this group had rapidly progressive disease and all died within ten days following admission to the hospital. Deaths and age distribution in the active cases are reported for this survey: 16 patients under 1 year of age, 7 deaths, 21 patients between the ages of 1 and 2 years, 16 deaths, 22 patients between 2 and 3 years, 10 deaths; 14 patients between 3 and 4 years, 5 deaths; 20 patients between 4 and 6 years, 7 deaths; 15 patients between 6 to 8 years, 3 deaths, and 8, patients 8 to 10 years of age, 4 deaths. In those patients who succumbed to the disease, death usually occurred within three months from the time of the first noted symptom referable to tuberculous infection Tuberculous bronchial pneumonia was a common finding in the African children, being the principal cause of death in 29 of 47 tuberculous children who came to autopsy The mortality rate among children with tuberculosis in this area is extremely high, especially in those under three years of age. The onset of tuberculous bronchial pneumonia followed by rapid deterioration suggests that this African population has very little resistance to the organism

Bronchial involvement by tuberculous hilar nodes as a complication of primary tuberculosis has been emphasized recently in this country (84) Bronchiectasis in later life which may result from such involvement, was avoided in some instances by prompt bronchoscopic removal of the obstructing granuloma and by the use of antibiotics Recent emphasis has been placed, likewise, on the importance of thorough history and careful differential diagnosis since chronic nontuberculous infections of the lungs may simulate tuberculosis in symptomatology and roentgenographic appearance. Since nonpathogenic acid-fast bacilli may be ingested with food and drink, the finding of acid-fast organisms in the gastric contents does not in itself constitute evidence of tuberculosis With few exceptions, a persistently nega-
tuberculo-
pulmonary
charge was
void risk of

general, hemorrhagic manifestations are mild; they may appear in very early life, depending on circumstances. In childhood and later life, bleeding from relatively minor trauma, following loss of teeth or minor surgery, may be considerable. Hemarthrosis is not a characteristic finding. In hemophilia-C clotting time may be prolonged; prothrombin consumption test shows deficiency in utilization of prothrombin; and mixed blood tests show that plasma from C-patients corrects deficiencies in plasma of either A or B patients. While the bleeding tendency is less marked in hemophilia-C, treatment may be urgent in order to prevent continued loss. Since PTA is a relatively stable factor, stored or banked blood or plasma may be adequate for control of the hemorrhagic tendencies.

While in all three types, normal plasma or blood is the chief means of corrective therapy, differentiation of these hemorrhagic diatheses is still important from the standpoints of diagnosis, therapy, and prognosis (94). Hospital laboratories are now setting up procedures routinely which will aid in the recognition of these deficiencies. Research laboratories are attempting identification and evaluation of the various clotting factors by means of electrophoretic studies. Interesting fundamental studies are being carried out in the dog which have served to clarify some of the mystery surrounding these hemorrhagic diatheses, particularly with reference to genetic factors and the dynamics of the various clotting mechanisms (95, 96).

antihemophilic globulin in the treatment of hemophilia. To date, however, the substance has not been released for general use because of its antigenic potentialities (89).

The development in the blood of hemophilic patients of anticoagulant substances presents a serious therapeutic problem which is being observed with increasing frequency, especially following repeated transfusion (90). Cortisone and ACTH have been used in an attempt to diminish the activity of the circulating anticoagulant against AHG, and in some hands such treatment does seem to have resulted in better therapeutic effect in plasma transfusions. Such observations concerning the development of anticoagulant substances emphasize the importance of protective measures and local hemostatic measures wherever possible, surgical closure of even superficial wounds, powdered thrombin, or other topical hemostatics, judicious local pressure, etc.

Control and treatment of hemarthrosis is of great importance if serious crippling is to be avoided. Following control of the hemorrhage, acute joint conditions have been treated with some success by the use of hyaluronidase, known to decrease viscosity, increase permeability, and hasten the absorption of blood from the joint (91). Cautious local therapy by heat, pressure, passive exercise, massage, and the like, is employed, as indicated in the individual case. In last analysis, each case, or episode, must be individualized, and the care of the hemophiliac depends largely upon the judgment of the physician in charge.

Hemophilia B, Christmas disease, described as resulting from an inability to form PTC,[2] is also considered a sex-linked recessive factor, thought to be located genetically at a different x-chromosomal locus from that to which true hemophilia is referable. Apparently its occurrence in females has not been recorded to date. Preliminary statistical studies suggest that about 20 per cent of known hemophiliacs may be suffering from the B-type. Clinically these two hemorrhagic diatheses are difficult to differentiate, and in both the wide range of severity of symptoms includes bleeding into tissues and crippling joint manifestations Mild episodes may occur in both types. Tests reveal that both conditions are characterized by inadequate activation of thromboplastin, and special laboratory procedures are required for identifying the particular deficiency The distinction may be made, however, by the fact that the B-plasma corrects *in vitro* the coagulation defect of A-plasma While therapy in hemophilia-B is essentially similar to that in classic hemophilia, one important difference facilitates therapy, the fact that PTC is comparatively stable in stored, banked plasma, or blood, so that the fresh whole blood or plasma required for the true hemophiliac is not needed for the patient suffering from the B-type (92)

Hemophilia-C, inability to form adequate PTA,[3] is likewise a familial disease, thought to be inherited as a Mendelian autosomal dominant, i e, not sex-linked, affecting potentially both males and females. Three recorded patients were members of the same family, two females, one male (93). In

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ENDOCRINOLOGY[1,2]

(Relationships between the Endocrine and Nervous Systems)

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Endocrinology pervades all areas of physiology and medicine The endocrine system serves as an adjunct to the nervous system which is the chief integrating and regulating mechanism of the body functions While the nervous system carries out its function by the transmission of impulses along fibers, the endocrine organs and tissues secrete humoral agents which reach their targets by way of the vascular system Whereas the nervous system acts to integrate the functions of tissue masses, organs and the body as a unit, the endocrine system is primarily concerned with integration of the metabolic processes of tissues and cells and in general finds its sites of action at the cellular level.

The review of detailed, often unrelated contributions in the arbitrarily circumscribed field of endocrinology has been well-covered during recent years in other volumes of *Annual Reviews* (1–8). An effort has been made here to limit the discussion to three aspects of the subject, namely, the influence of the endocrine system upon the nervous system, the control of the endocrine system by the nervous system, and the question of stress and adaptation as it relates to these two integrating mechanisms. This means that in reviewing subjects rather than the literature of a calendar year the literature cited is not all recent.

Influence of the Endocrine System on the Nervous System

Although the endocrine system is an adjunct of the nervous system in the regulation of the body functions, hormones or lack of hormones have a marked influence on the nervous system This influence may be actuated through changes produced in the internal environment (e g , anoxia, increased oxygen concentration, blood sugar level, etc.) or as a result of variations in cell metabolism, i e , at the enzyme level. So far little is known of the last and most likely possibility In support of this there is much evidence for the action on cells outside of the nervous system Examples are the influence of corticoids on the enzymes of carbohydrate metabolism (9) and the effect of steroids on tissue oxidation (10). It has been proposed (11) that thyroid hormones might regulate metabolic rates by varying the efficiency with which cellular oxidations are coupled with phosphorylations (12).

Most of our present knowledge about endocrine influence on the nervous system has to do with the cerebral cortex and to a less degree with the brain

[1] The survey of literature pertaining to this review was concluded in October 1954.

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The thyrotropic hormone (TSH) of the anterior pituitary is not the cause but an exophthalmic producing substance (EPS) has been demonstrated in the plasma of patients with exophthalmos (28 to 31) and has been isolated from extracts of the anterior pituitary.

If the production of the thyroid hormone is reduced below the requirement of the body, characteristic phenomena, which are known as hypothyroidism, myxedema, and cretinism, result. These conditions may result from primary failure of the thyroid gland or be secondary to inadequate stimulation from the thyrotropic hormone of the anterior pituitary. In any case the lack of hormone has a profound effect upon the nervous system In children there is marked mental retardation and in adults sluggishness. Myxedema is claimed to be one of the most important causes of organic psychoses (32) The reduced excitability is not limited to the cerebral cortex but is found in all functions of the nervous system (32, 33)

Parathyroids—Hypoparathyroidism affects the nervous system primarily because of low concentration of ionized calcium in the plasma (34, 35, 36). Tetany is the most common finding but epileptic attacks, mental retardation, psychiatric disturbances, papilledema, cerebellar dysfunction, and electroencephalographic abnormalities occur (37, 38). Hypoparathyroidism has even presented itself as a dementia (39)

The clinical manifestations of the neural effect of hyperparathyroidism are those of hypercalcemia It leads to hypotonia, lassitude, a sense of mental depression, and, when marked, to vomiting, dizziness, and coma (40).

Pancreatic islets—The typical action of insulin on the nervous system is found when there is an excess and hypoglycemia results. Since the brain depends on glucose as a source of energy, it is profoundly affected Convulsions (used for psychiatric therapy) and eventually cerebral edema or even permanent brain damage may occur (41)

In the diabetic there is a relative deficiency of insulin possibly, in some instances, because of an excess of the hormone glucagon which arises from the alpha cells of the pancreatic islets (42, 43, 44). Glucose utilization is interfered with and, since all nerve cells depend on it for energy, the occurrence of neuritis in the uncontrolled diabetic is not surprising (45, 46) Autonomic neuropathy simulating sympathectomy has even been described as a complication of diabetes mellitus (47).

Adrenal medulla—Epinephrine and norepinephrine are secreted by the adrenal medulla which is actually a huge specialized sympathetic nerve ganglion In adult man epinephrine predominates Adrenomedullary activity is stimulated by sympathetic nerve impulses The first action of epinephrine discharge on the nervous system is that of reinforcing sympathetic stimuli (48). Subsequently it reduces sympathetic stimuli by ganglion blockade (49, 50, 51) and reduction of the excitability of the hypothalamus (52, 53) Eventually it inhibits *the release of epinephrine by the adrenal medulla itself* (54) There is little doubt but that the effect of epinephrine is a direct one

Adrenal cortex.—The hormones of the adrenal cortex directly or indirectly

stem. As for the spinal and peripheral nerves there is as yet a paucity of information.

Thyroid —The classical example of the influence of the endocrine system, i.e., the thyroid hormone, is *seen in hyperthyroidism and hypothyroidism* Hyperthyroidism affects all of the cells in the body but has the most startling effect on the nervous system The typical clinical picture is quoted from Levitt:

> "The central nervous system is unstable and there are exaggerated emotional responses and tremor. Undue haste, anxiety and insomnia are associated with a rapid flow of thoughts and excited dreams Nervous breakdowns are frequent Psychosis may be of a true type, occasionally culminating in hallucinations, mania and melancholia The sympathetic nervous system shows characteristic vasomotor instability. Hot flushes are frequent. The alimentary system is affected by increased peristalsis or even diarrhea" (13).

Whether the *thyroid hormone acts directly on the nerve cells or indirectly* by way of its influence on other tissues is a point which requires further elucidation. Asher & Flack (14) showed long ago that this hormone increases the susceptibility of nervous tissue to epinephrine The effect of the thyroid hormone on cerebral cortex activity is well-known An excess increases the alpha frequency of the electroencephalogram. Moreover, in hypothyroidism as well as hyperthyroidism the alpha frequency is related to the metabolic rate (15, 16) The sensitivity of the brain to anoxia is increased in hyperthyroidism (17). The intensification of conditioned reflexes by excess thyroid hormone (18, 19), the increased sensitivity of the light reflex (20), and the augmented response of the centers of the sympathetic nervous system (21) *show that the excitability of all parts of the nervous system is raised*

The mode of action of the thyroid effect on any cell, nerve or otherwise, is uncertain Many investigators have tried to demonstrate an effect of the thyroid on tissue slices *in vitro* without success. Thyroxine is usually *chosen* for such studies and it is possible that this compound is not the final active principle of the thyroid (22, 23) and only in the intact organism does normal degradation take place

Recently Lardy & Maley (12) have shown thyroid effects on the metabolism of isolated liver cell mitochondria Although the hormone does exert a direct effect in all the tissues of the body there is much old evidence, largely clinical, that the main effect takes place in the hypothalamus (24) Action of the thyroid hormone on the nervous tissues of the brain has been interpreted as being due to a rise in brain metabolism Data on this point are controversial (25) Sensenbach *et al* (26) have shown that cerebral blood flow is increased in hyperthyroidism and reduced in thyroid deficiency but the rate of glucose and oxygen consumption is unaltered in either case.

Exophthalmos is characteristic of many cases of hyperthyroidism. The mechanism has long baffled investigators (27) The thyroid hormone is not directly responsible and a neural mechanism has not been demonstrated.

Hypopituitary coma has since been discussed by others (77 to 82). Whittaker & Whitehead (83) have recently described two cases and Caughey & Garrod (84) have described a variety of factors precipitating disturbances of consciousness in hypopituitarism. Disturbances of consciousness vary from hypersomnia, mild confusion, and impaired cerebration to stupor and profound coma. It is not known whether the disturbances are due to connections the pituitary may normally have with the thalamus, hypothalamus and the reticular area of the mid-brain or are due to metabolic changes in these nervous tissues resulting from endocrine deficiencies which are directly a result of the lack of anterior pituitary hormones or secondarily from the loss of the effect of the secretions of other endocrine glands which are dependent on the pituitary. The last possibility appears to be the most likely and all cases of hypopituitarism have failure of adrenal cortex function. Surgery of the pituitary gland, hemorrhage into this organ, infections, hypoglycemia, hypersensitivity to drugs and anesthesia, sodium depletion, water retention, cerebral anoxia, and hypothermia may all precipitate disturbances of consciousness in such patients

Many of the disturbances described under deficiency or hyperfunction of the adrenal cortex occur with similar disturbances of the anterior pituitary. The pituitary hormone ACTH when given in excessive doses also mimics most of the effects of pathological doses of cortisone

Posterior pituitary—There is no good evidence that the hormone (or hormones) of this neuroendocrine gland act on any part of the nervous system Used in excess these hormone preparations may produce water intoxication and the symptoms which accompany it. Posterior pituitary hypofunction leads to diabetes insipidus with excessive loss of water through the kidneys and a tremendous thirst. Water restriction leads to severe dehydration and manic behavior as in any such desiccation

Ovaries—Like the steroid hormones of the adrenal cortex no direct influence of the estrogens and progestin has been demonstrated on nerve cells Clinically the effects on the nervous system are quite marked. We have examples in the depressions often accompanying the high hormone titer preceding the onset of menstruation, disturbances of the high nerve centers during pregnancy, the signs and symptoms of the menopause and the profound effect upon the mind of estrogen therapy used for cancer of the prostate in the male Whether the female sex hormones act directly upon the cells of the nervous system or produce changes secondary to alterations in the tissue milieu must await further study.

Testes—Androgens have a striking effect on the ailing male with failing gonadal function The improved functioning of the cerebral cortex comes about by an unknown mechanism which may have little to do with a direct interaction between the androgen and nerve cells

Control of the Endocrine System by the Nervous System

The influence of the hormones of the endocrine system upon the nervous

affect occurrences in the nervous system. This has long been evident in the changes incident to the adrenal insufficiency of Addison's disease and the hyperactivity of the cortex in Cushing's syndrome. In recent years the neural effects of the administration of adrenal cortex extracts and the synthetic hormones such as desoxycorticosterone, cortisone, hydrocortisone, etc. have been emphasized.

In hypofunction of the adrenal cortex the nervous manifestations may be quite vague. Drowsiness often accompanies the progressive weakness and at times the patient is restless and irritable but there is nothing characteristic about these symptoms. Hyperfunction of this gland commonly leads to mental depression and psychoses have been observed which closely resemble either the depression phase of manic-depressive psychosis or involutional melancholia (55). Euphoria, mental elation, depression, irritability, restlessness, and insomnia are found in patients undergoing cortisone or ACTH therapy, and the occurrence of severe mental disturbances including psychoses in some patients when taking large doses of cortisone or ACTH over extended periods of time is not uncommon (56 to 62). Many patients with adrenal tumor have psychoses, and psychiatric disturbances often accompany hyperplasia of the adrenal (63). The hypoadrenalism of many Addisonian cases may also be accompanied by psychosis (64). Desoxycorticosterone has an anticonvulsant action in relation to idiopathic epileptic seizures (58, 60, 65) Hoagland has summarized much of his data and that of others from this viewpoint in an excellent review (66)

In most patients with adrenal hypofunction abnormalities are found in the electroencephalogram, including oscillations slower than normal rhythm (particularly in the frontal areas), absence or decreased number of beta waves, and increased sensitivity to hyperventilation (67) The slowing in frequency of the electroencephalogram is restored by cortisone (68, 69) and the latter even increases the frequency of the alpha rhythm in patients without hypoadrenalism (70). The convulsive threshold of the brain is lowered after adrenalectomy but is restored to normal by desoxycorticosterone or sodium chloride (71). When administered in excess to the normal animal, desoxycorticosterone raises the convulsive threshold and the effect may be counteracted by cortisone (72, 73) There is an excellent review (74) which evaluates the influence of the adrenal cortex hormones on electrolytes and fluids in the body (also see 66). Woodbury reviews the effect of hormones on brain excitability and electrolytes (75)

There is little evidence to indicate that the adrenal cortex hormones directly affect the nervous system It seems likely that the changes are due to altered electrolytes, blood sugar, etc , leading to modifications in the environment of the nerve cells

Anterior pituitary—There are many indications that a normal active pituitary is essential for the maintenance of consciousness In an early account of hypopituitarism Simmonds (76) described a patient who was subject to attacks of unconsciousness.

fails to occur after splanchnectomy (108) or adrenalectomy (109) Hemorrhage, anoxia, asphyxia, hypoglycemia, various drugs, muscular exercise, and even the complex processes associated with emotion by direct or reflex action on the central nervous system lead to the release of the adrenal medullary hormone (110).

Anterior pituitary or adenohypophysis.—There are at least six different anterior pituitary hormones, namely, the pituitary interstitial-cell-stimulating hormone (ICSH), follicle stimulating hormone (FSH), adrenocorticotropic hormone I (ACTH I), adrenocorticotropic hormone II (ACTH II), thyroid stimulating hormone, (TSH), and pituitary growth hormone (PGH), (111, 112) The release of these hormones by the adenohypophysis is governed by three different mechanisms which may be unified in their ultimate end action. Anterior pituitary secretion is controlled to some extent by a "feed-back" action of the hormones of the other endocrine glands (gonads, thyroid, and adrenal cortex) which depend on it for their normal integrity (113, 114). It is because of this mechanism that these endocrine glands atrophy in hypopituitarism due to complete destruction of the adenohypophysis (115) At present it is uncertain whether the hormones of the adrenal cortex, gonads, and thyroid act directly on the anterior pituitary to govern the release of the hormones which control these glands or function via neural stimuli (86, 116) However, the maintenance of the adrenal cortex in the absence of hypothalamic influences would indicate that one endocrine balance may be integrated in the pituitary itself (117).

A second and probably secondary factor in the regulation of the secretion of the hormones of the anterior pituitary is the effect of epinephrine which is secreted by the adrenal medulla in response to activity of the sympathetic nervous system. It has been shown to cause the secretion of one of the adrenocorticotropic hormones There has been some question as to whether epinephrine is a stimulator of the anterior pituitary in man (118, 119, 120) as it is in lower animals However, adrenal stimulation has been demonstrated by the infusion of epinephrine into the human and the fact that this is followed by a period of blockade (121) is what might be expected from the known actions of epinephrine (49–53). Furthermore, epinephrine effects the release of ACTH in a primate (122) In spite of all the evidence in the rat (124, p 318–26) that epinephrine may act directly on pituitary tissue to cause the release of ACTH, it seems clear that the integrity of the hypothalamus is necessary in a primate (122) Here at least the action of epinephrine on the anterior pituitary is via a neural route. There is an alternative to the conclusion that epinephrine may act directly on the pituitary tissue Epinephrine might cause a lowering of the adrenocortical hormone level in the blood and tissues and this decreased concentration would act upon the pituitary to cause hormone release, a mechanism that is well-recognized In any case the hypothalamus would be involved for it is as a result of stimuli from sympathetic centers in this part of the brain that epinephrine is secreted by the adrenal medulla

With the possible exception of the maintenance of its dependent endo-

system is for the most part a general one while the action of the nervous system on the endocrine organs is more specific. The nervous system actually exerts a large measure of control over the endocrine system.

Posterior pituitary or neurohypophysis.—The role of nervous impulses in the secretion of hormones is probably greater for the posterior pituitary than for any other endocrine tissue (85 to 88). Excitation of the gland can result from emotional stress. Hemoconcentration, physical exercise, and a variety of noxious drugs have the same effect (89). It is not certain whether the antidiuretic and oxytocic principles are one or multiple hormones The control of the secretory activity of the neurocytes in the posterior pituitary is abolished by cutting the pituitary stalk, interruption of the fiber tracts leading from the supraoptic and paraventricular nuclei of the hypothalamus, or destruction of these nuclei Not only is no antidiuretic hormone secreted but the amount in the gland is rapidly diminished

Of considerable interest is the manner by which nervous stimuli from the hypothalamus reach the posterior pituitary. It may be by orthodox nerve fiber transmission (90), through a neurohormone or via neurosecretions The latter appear to serve as vehicles for hormones but neurosecretions and hormones are not identical (91, 92, 93). The Scharrers (94) have presented evidence that neurosecretory cells in the hypothalamus actually manufacture the hormones which are then carried down the stalk to the posterior lobe where they are stored. Support of this view is provided by other newly reported data, chiefly histochemical, relative to neurosecretory activity in the supraoptic and the paraventricular hypothalamic nuclei (95, 96) and the hypothalamo-hypophyseal system (97–100)

Adrenal medulla.—It has already been pointed out that this endocrine gland is actually an enormous specialized sympathetic nerve ganglion Although there are stimuli which cause the denervated adrenal medulla to release its hormone (chiefly epinephrine), the quantity set free is small and of little consequence in comparison with the amount of epinephrine entering the blood stream when stimuli reach it via the sympathetic nervous system Cannon (101) showed long ago that the chief function of the adrenal medulla was the adjustment of the rate of epinephrine secretion to conditions of emergency after which it ultimately quiets sympathetic stimuli (49, 50, 51) and the excitability of centers in the hypothalamus (52, 53)

The secretion of epinephrine is regulated by autonomic centers in the hypothalamus and medulla oblongata, the spinal centers playing a subordinate role Stimulation of the postero-lateral hypothalamic area induces a secretion of epinephrine (102, 103) An even greater influence must be attributed to the medulla oblongata (104) The spinal sympathetic centers can be excited directly or reflexly to induce epinephrine secretion (105–107).

Cannon and his school (101) established the fact that a variety of conditions call forth the secretion of epinephrine As an example, cold increases the blood sugar by a central autonomic discharge which stimulates the adrenal medulla The released epinephrine acts in the liver to cause the formation of glucose from glycogen This secretion of epinephrine due to cold

rotropic hormones, one of which regulates hyperplasia of the thyroid and is under hypothalamic control and a second involved with the function of the gland which is related only to the anterior pituitary.

Werner (140) has summarized the evidence that hyperthyroidism in man (Graves' disease) is not due to an excess of thyroid-stimulating hormone released by the anterior pituitary but rather that the normal reciprocal relation between the pituitary and the thyroid appears to be disrupted with the thyroid assuming functional autonomy. Granting the existence of Greer's thyroid hyperplasia hormone, it is interesting to speculate on what a disturbance in hypothalamic function which gave a hypersecretion of this hormone might lead to.

Ovaries and testes —The gonads of both sexes are maintained anatomically and regulated functionally by the anterior pituitary (141, 142) The follicle-stimulating hormone (FSH) causes germinal cell production and maturation, i e, follicle maturation in the ovaries and germinal epithelium maintenance and sperm-maturation in the testes The luteinizing hormone (LH) or interstitial cell-stimulating hormone (ICSH) causes corpus luteum development in the ovaries and Leydig cell development in the testes. The lactogenic or luteotropic hormone (LTH) is responsible for lactation at the termination of pregnancy and is necessary for the stimulation of the functional activity of the corpus luteum which probably produces estrogens and progesterone. This third gonadotropin (LTH) has no established action in the male. The two gonadotropins, FSH and LH or ICSH, govern secretion of estrogens by the thecal and granulosa cells of the corpus luteum of the ovaries and androgens by the Leydig cells of the testes. The FSH also stimulates spermatogenesis in the testes The secretion of the several tropins by the anterior pituitary is regulated by the effect on it of the hormones (estrogens, progesterone, androgens, etc.) produced in the dependent glands Estrogens, unlike any of the other hormones which are secreted via an anterior pituitary tropin, have the power, in high doses at least, to inhibit not only gonadotropin secretion but also secretion of the growth hormone, the thyroid-stimulating hormone and one of the adrenocorticotropins Estrogens are responsible for the growth and development of the internal and external female genital organs (143). In addition along with progesterone they cause the cyclic changes evinced by menstruation, lead to development of the breasts and secondary sex characteristics, and play a large part in alterations of body functions during pregnancy Their decrease or absence underlies the onset of the menopause The male sex hormone sets in motion the bodily changes known as puberty, the maintenance of sexual function in the adult, and has definite metabolic actions

Evidence for the control of the gonads by the central nervous system, i e, cortical or reflex stimuli reaching the anterior pituitary by way of the hypothalamus, is very meager for man. However there is a large bulk of indirect clinical evidence for central nervous system control It is a common observation that emotional upsets or nervous disorders frequently affect

crine glands at a routine level, the secretion of hormones by the anterior pituitary is under the control of the central nervous system (113, 114, 122, 123, 124) The mediator of stimuli from the hypothalamic region to the anterior pituitary is still a matter of conjecture At present it is assumed that the effect is through a neurohormone which passes to the pituitary by its portal circulation (125, 126).

There is considerable clinical evidence that both the control of release, and the origin within the gland, of the various anterior pituitary hormones is highly individualized. In hypopituitarism due to post partum necrosis there may be specific hormone failure as well as a general decrease in all of the hormones (127, 128) Hubble (128) divides hypopituitarism into psychogenic, nutritional, and genetic types. The first two groups have widely varying hormone lacks The genetic group includes those instances in which a developmental defect causes a deficiency or absence of one of the anterior pituitary hormones Examples include hypogonadotropic hypogonadism (129), hypothyrotropic hypothyroidism (130, 131), dwarfism (128, 132), and hypoadrenocorticotropic Addison's disease (133) The sodium retaining corticoid (electrocortin or aldosterone) of the adrenal cortex is apparently not under the control of the anterior pituitary (134).

Adrenal cortex—The adrenal cortex has no nerve supply but the secretion of hormones (except the sodium-retaining corticoid) by this gland is so dependent upon the anterior pituitary that the strong control of the latter by the central nervous system indirectly places the adrenal cortex hormones under the same control.

Thyroid—The thyroid gland is richly supplied with both sympathetic and parasympathetic nerve fibres They apparently have vasomotor functions and are not true secretory nerves but may influence the functions of the follicular cells by altering their blood supply The real control of the thyroid gland by the central nervous system is by way of the anterior pituitary and the thyroid-stimulating hormone which it secretes This hormone is essential for the structural and functional integrity of the thyroid gland. The secretion of the thyroid-stimulating hormone is only partially dependent on the hypothalamus For the most part secretion by the anterior pituitary is dependent on the concentration of the hormone in the plasma to which the rate bears an inverse relation. That there is some regulation of the secretion of the thyroid-stimulating hormone by the central nervous system is shown by the reduced thyroid activity and failure of exposure to cold to increase it after complete transection of the pituitary stalk (135) The usual changes in the basophil cells of the anterior pituitary which follow thyroidectomy fail to occur if transection of the stalk precedes removal of the thyroid (136) Greer (137) found that hypothalamic lesions between the optic chiasma and the infundibulum prevented the hyperplastic response to goitrogens but did not interfere with the elevation of the thyroid-serum iodide concentration ratio This existence of hypothalamic sites involved in thyroid regulation has been confirmed (138). This has led Greer (139) to conclude that there are two thy-

the part of the organism to maintain homeostasis (161). This may be a stimulus arising from some internal source in the body with no immediate relation to the external environment or one of the innumerable stimuli to which the organism is continuously exposed in its environment. As a matter of fact life is a continuous succession of stresses and multiple stresses. Some of them are desirable and many are obnoxious to the organism. The body has many ways of dealing with them. Most of the adjustments to the stimuli which we call stress are brought about through the action of the central nervous system and the endocrine system. A large part of the activities of the latter are controlled by the nervous system.

Adjustments made to stress by the organism may lead to adaptation. When this occurs exposure to further stress of the same kind may be more easily dealt with by the body, i e., the repeated stimuli finally require less or no adjustment, and little or no action on the part of the nervous system or endocrine system is required or carried out.

Although other physiologists had some conception of the reaction of the body to stress Claude Bernard (162) was the first to state the essentials of the process Cannon (48) enlarged this concept as an "Organization for Physiological Homeostasis" At that time he stressed the functions of the divisions of the autonomic nervous system such as the "sympathico-adrenal" and the "vago-insular" influences. Elsewhere Cannon (163), referring to the autonomic nervous system, summarized its function as follows: "The most general descriptive statement which can be made regarding the service of the autonomic system is that its prime function is the maintenance of stability or homeostasis in the fluid matrix of the organism." In later years the autonomic nervous system was more or less placed in limbo as far as stress was concerned. Selye (164) managed to push the adrenal cortex-pituitary gland relationship into the position of explaining all facets of stress. Quoting Cleghorn (165):

> Because the adrenal cortex has lent itself in recent years to intensive study there has been a tendency to think of the body as an animated adrenal gland, an attitude which received just admonishment from Loeb (166) at the 1949 meeting of the Association for Research in Nervous and Mental Diseases on Life Stress and Bodily Disease

It is now possible, since the neural control of the anterior hypophysis via the hypothalamus has been so clearly demonstrated (90, 125, 148, 167, 168, 169), to consider again the reaction to stress in its proper light—primarily a response of the central nervous system, particularly the autonomic divisions. Modification of insulin secretion by parasympathetic innervation of the pancreas, control of epinephrine and norepinephrine secretion by sympathetic innervation of the adrenal medulla and control of the secretion of the hormones from the neurohypophysis by nerve impulses from the hypothalamus has been outlined earlier. Neurohumoral control of the adenohypophysis by centers in the hypothalamus and secondary control by tropic hormones of

ovarian function, often resulting in functional disturbances of the menstrual cycle Sterility in the female is frequently associated with nervous disease and psychic upsets. Brain lesions or tumors involving the region of the third ventricle and the hypothalamus have been found to be associated with precocious puberty (144). Disturbances of the nervous system, both functional and organic, can interfere with libido and potency (145). Psychoneuroses often influence sex activity in a way which resembles the changes found in the relatively rare syndrome, the male climacteric (146).

Ovulation is definitely influenced by the nervous system via the anterior pituitary (124, p 307–8). A recent study stresses neurogenic activation of the pituitary in ovulation (147) Harris (148) believes that neurohumoral transmission accounts for the effect of neural centers on the anterior pituitary in regulating ovulation. Markee and his collaborators (149–152) have presented interesting evidence in this field

Pancreas—Insulin, which disposes of sugar, is secreted by the endocrine tissue of the pancreas Since insulin secretion depends on the blood glucose concentration, such nervous control of the adrenal cortex or other tissues which yield hormones affecting the blood sugar level will give a measure of very indirect control of insulin secretion by the pancreas. Fibers of the right vagus nerve innervate the islets of Langerhans in the pancreas which secrete insulin Stimulation of this nerve leads to insulin secretion. Hypoglycemia causes insulin secretion if the thalamus and hypothalamus are intact (124, p 292–93). The presence of the cerebral cortex is unnecessary Anoxia, cold, fever, histamine, etc, stimulate both the sympathetic and parasympathetic nervous systems, the first releasing epinephrine and causing hyperglycemia while the latter stimulates the islet cells directly, causing them to release insulin The hyperglycemia usually triumphs but in the absence of the adrenal medulla hypoglycemia results (153 to 157)

THE CENTRAL NERVOUS SYSTEM AND THE ENDOCRINE SYSTEM AS THEY AFFECT STRESS AND ADAPTATION

"Although neither the central nervous system nor the endocrine glands are essential for the life of the individual cell or organ, they are essential for those changes in the reaction velocities of the intracellular enzyme systems which enable the organism to grow and develop and to adjust readily and rapidly to environmental vicissitudes The mechanisms whereby nervous and humoral factors regulate intracellular activities remain unknown Although it is possible that both systems may act directly on specific enzyme systems, there is much to suggest (158, 159) that they act principally by influencing the permissiveness or responsiveness of the cell to its own environment Many examples suggest that the reaction to any stimulus, be it neurological or hormonal, is dependent upon the state of the cells which in turn is determined by the continuous interactions between the effects of neural impulses and the effects of hormones" (160)

Stress has been defined as any stimulus which requires an adjustment on

petite, a feeling of general well-being and normal fertility (P. Ehrlich cited in 180). Complete, but not partial, acclimatization produces a balanced state of homeostasis (181) Acclimatization to chronic exposure to low oxygen tension (182, 183) is much more complete than that to intermittent exposures (184 to 187) Whether intermittent stress is actually detrimental is open to question (188-193)

Adaptation to chronic hypoxia is brought about by increased ventilation of the lungs originating in respiratory centers of the medulla of the brain, an increase of the oxygen content of the blood because of polycythemia, and a tremendously increased vascularization of many tissues (180). The mechanism of the adaptation is of course complex. Hypoxia changes the acid-base balance (194) via its effect on the expired air and kidneys and this in turn acts on the respiratory center in the brain. The origin of the polycythemia is not known but could be via the hypothalamus—anterior pituitary—(thyroid and gonads) (195). Just how the increased vascularization is brought about is unknown but it could well be due to local cell reactions based on oxygen need versus supply. The adrenal cortex apparently plays little part in adaptation to hypoxia except perhaps in the early stage when the carbohydrate demands of the organism are being adjusted (180) Even here it has been pointed out (196) that the adrenal cortex may not induce the changes in carbohydrate metabolism characteristic of hypoxia, but rather that the changes may be initiated by tissues whose functional activity requires the presence of the cortical hormone.

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the adrenal cortex, thyroid and gonads are now well accepted. The chief integration of the activities of the organism in response to stress is certainly within the central nervous system although much of the action may be carried out by the sympathetic division of the autonomic nervous system and the secretions of the endocrine glands under nervous control.

Adrenal cortex.—The hormones of the adrenal cortex are important end results of the reaction of the nervous system to stress. Adrenal cortical hormone is necessary but not responsible for the metabolic response to stress (170). Ingle (171) believes that adrenal cortex hormone supports a variety of metabolic and other reactions which are primarily determined by the needs of the tissues and are designed to maintain homeostasis. Responses to stress can occur in the face of a controlled and constant supply of cortical hormone (172). This is of course contrary to the former widely held view that response to stress is non-specific. Conn and his co-workers (173) have shown that stressor agents are capable of exerting some specific effects on man. Cleghorn (165) has found that the responses to pressor drugs and sympathetic nerve stimulation are impaired by adrenalectomy. Goldstein & Levine (174) have not only demonstrated that the adrenal corticoids are necessary for norepinephrine vasoconstriction but that eosinopenia and fat mobilization are steroidal effects involving epinephrine at the peripheral site of action. They believe that many adjustments to stress involve this cooperative action at the level of responding tissues and that the anterior pituitary stimulation of the adrenal cortex is a secondary physiologic exaggeration of corticoid supply. It is further suggested that the corticoids sustain tissue reactivity to the epinephrines and protect tissue integrity in responding to elevated levels of epinephrine exhibition. Beyond this, it is proposed that heightened autonomic adjustments occur in stress and are paralleled by increased hypothalamic-adenohypophysis-adrenal cortex activity in providing additional steroids for support and protection of tissues responding to the epinephrines. In this connection the influence of ACTH and epinephrine on fasting levels of eosinophils, blood glucose, and 17-hydroxycorticosteroids is quite different (175).

Emotional stress.—Cannon's early work (101) on stress was largely concerned with emotional stimuli. Subsequent workers tended to use physical and chemical stimuli. These are useful but in man at least psychosomatic relationships are probably much more important. As witness of this is Dunbar's herculean review (176) of over 4700 papers on "Emotions and Bodily Changes" which have appeared since 1910. Recent studies in this field (160, 161, 177, 178, 179) have tended to deal rather exclusively with adrenal cortex but her survey emphasizes the need for giving attention to the primary aspects of the problem.

Adaptation.—A thoroughly studied example of adaptation to one kind of repeated or continuous stress is acclimatization to low oxygen tension, or hypoxia (180). The criteria for full adaptation in this case are maintenance of growth in the young, maintenance of nutrition in the adult, no loss of ap-

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DISEASES OF THE URINARY SYSTEM (SURGICAL)

(Diagnostic and Operative Techniques for the Urinary System)

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In surgery, as in other fields of science, new concepts are created by new procedures Advance depends upon the introduction and the progress of new techniques, which increase our diagnostic acumen, lower mortality and morbidity rates, and produce more satisfactory end results A few of these innovations are considered here.

Experiments in the perfusion of living organs and tissues with blood circulated by a pulsating mechanical apparatus gradually led to a better understanding of the internal environment of the body (1) Failure of the proper functioning of the kidney, which bears the greatest responsibility for maintaining this internal environment at its best functioning level, threatens life Vividialysis (2) was introduced to substitute for the work of the kidney and to restore the proper balance of chemicals within the internal environment of the body. Peritoneal lavage (3), intestinal lavage, and artificial diffusion through a cellophane membrane, the so-called artificial kidney (4, 5, 6), all have merited and received close attention. Each has been used to help restore function through the removal from the body of toxic substances which would readily have been cleared by normal renal action In very carefully selected cases restoration of function has been most frequently accomplished by the artificial kidney However, with this instrument there are dangers from overhydration, from heparin poisoning with resulting hemorrhage, and from the washing out of essential substances along with the undesirable ones.

Transplantation

Better adapted to a surgeon's idea of things is renal homotransplantation (7) In dogs the duration of functional survival of such homotransplants of kidneys is about five days with an upper limit of about three weeks It is generally thought that antibodies, created in the host by substances in the transplanted organ, close the vessels running into the transplant and cause its death and elimination from the recipient's body. In man the only successful homotransplants excepting corneal transplants have been from the body of one identical twin to the other. A recent clinical experiment has renewed interest in the fascinating possibility of renal homotransplantation in man. In a case report by Gustave J Dammin and his associates (7), functional survival in renal homotransplantation is described as having lasted almost six months Quoting from their own abstract

> The patient, G W , was a 26-year-old physician with terminal chronic glomerulonephritis The homotransplant, from an adult patient who died during a cardiac opera-

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can clearly be demonstrated. In renal tumors this pattern is altered in a very characteristic way. Nodules are revealed in which there are irregularly distributed masses of vessels. Within some of these nodular areas there are poorly-defined blurs representing areas of extravasation. Cysts, on the other hand, appear as round, clear, avascular spaces from which the blood vessels have been pushed aside by the accumulated fluid which fills the cyst. Twelve per cent of such cysts are associated with malignancies deeply placed in the base of the cyst itself. Aortography cannot be expected to reveal such areas of malignancy. By combining aortography with perirenal air insufflation one more step toward the preoperative diagnosis of renal lesions is accomplished.

Experience with the use of an exploring needle in making aortograms and in obtaining deep tissue biopsies has brought closer the solution of a similarly difficult problem, that of the completely obstructed ureter. Ureteral obstructions, familiar to the urologist, may arise from stone, tumor, inflammatory strictures, operative injuries to the ureter, or pressure upon the ureter from without. If complete occlusion has occurred, intravenous pyelography may show no excretion of the dye into the renal pelvis. Retrograde pyelography may also be impossible because the blocked ureter may not permit the upward progress from bladder to kidney of either the ureteral catheter or of injected pyelographic medium, even though the medium is injected under pressure. The exact degree of ureteral and renal pelvis dilatation above the point of obstruction and the character and extent of the obstruction therefore remain undetermined. The usefulness of percutaneous renal puncture as a solution for problems of this type has been established (10). The introduction of a long, large-gauge needle into the renal pelvis directly from the outside through the skin and muscles of the back is not difficult. After the proper placing of the needle into the renal pelvis it is easily possible to pass a plastic tube into the renal pelvis through such a wide-gauge needle. This effects a temporary nephrostomy and permits restoration of function to the blocked kidney by allowing the constant escape of urine through the plastic tube. Such a tube may be left in place for months. The introduction of a pyelographic medium (11) through a needle so placed in the renal pelvis permits pyelography of great clarity as well as ureterography down to the point of obstruction, allowing a ready and accurate diagnosis to be made in what would otherwise be an obscure problem. The designation "percutaneous, needle puncture, antegrade pyelography" to distinguish this procedure from "retrograde pyelography" and from "intravenous pyelography," terms already in use, has been introduced by Casey & Goodwin (12) to describe this procedure of pyelography from above downward by means of a needle inserted through the skin and muscles of the back into the kidney pelvis.

Surgical Techniques

Close cooperation between abdominal surgeons and urologists in the working out and application of newly devised techniques of bowel and ureteral surgery has resulted in the successful use of isolated lengths of ileum

tion, was inserted into a polyethylene sac and placed subcutaneously into the thigh with vascular anastomoses to the femoral vessels and with a cutaneous ureteral orifice. Significant function appeared on the nineteenth postoperative day and for five months the homotransplant excreted between 1,500 to 2,000 ml. of urine per day. During this period, the patient's condition improved and the blood urea nitrogen dropped to 33 mg. per cent from an immediate postoperative level of 244 mg. per cent. The blood pressure remained elevated (220/140), congestive failure appeared, and the patient expired six months postoperatively.

Postmortem, the transplanted kidney weighed 340 grams. Vascular anastomoses were intact and endothelialized The ureter was slightly dilated and angulated. There was no pyelonephritis. The host epidermis had grown over the cutaneous portion of the ureter. The ureter was well vascularized and its smooth muscle intact. No cellular reaction was observed at the anastomotic junctions of host and transplant tissues. Since the other donor kidney was essentially normal, the advanced atherosclerosis with luminal narrowing observed in the smaller branches of the renal artery of the transplant must have developed during its tenure in the recipient.

Microscopically, the glomeruli were normal except for moderate basement membrane thickening There was advanced atrophy of the tubules particularly in the cortex. However, some tubules appeared normal or hypertrophied. There was advanced interstitial edema and moderate lymphocytic infiltration with some mononuclear cells showing pyroninophilia.

The long survival and morphologic changes observed suggest considerable compatibility of recipient and donor tissues and suggest that ultimate failure of the transplant resulted from vascular and circulatory changes related to hypertension and decompensation

This history-making experiment should greatly stimulate every worker interested in the field of homotransplantation and survival through renal transplants.

Diagnostic Methods

A technical achievement attained through the combination of precise surgical procedures and excellent x-ray technique is seen in the results accomplished by combined aortography (8) and retroperitoneal air insufflation There is a newly-devised method for the presacral injection of oxygen for retroperitoneal pneumography (9) in which the needle, through which air is to be introduced, is passed into the loose areolar tissue between the rectum and sacrum. In this method the air travels from that point upward to find its place within the retroperitoneal spaces around the kidney This method is proving to be less disturbing to the patient as well as more efficient than the earlier method of injecting retroperitoneally-placed air or oxygen through a needle which is passed through the skin into the perirenal fossa from a point just above the iliac crest. It has as yet brought about no reported fatalities. With these methods as well as with the aid of laminography, tumors of the adrenal have been localized and the difficult diagnostic problem of differentiating between cysts of the kidney which deform the pyelographic picture and tumors which produce closely similar deformities in the pyelogram has been solved. By means of aortography the normal vascular pattern

which has previously been detached from the bladder, freed and directed medially behind the sigmoid. Through the newly-made channel in the bowel wall the ureter is pulled into the bowel lumen. Delfino Gallo (19) of Mexico, who was the first to describe this method, also suggests splitting half a centimeter of the terminal end of the ureter and turning back a cuff of ureter This cuff he feels creates a valve and prevents reflux of gas and bowel content through the ureteral lumen upward into the renal pelvis The turned-back mucosal edge of the cuff is attached to the bowel mucosa by means of interrupted sutures of fine catgut The opposite ureter is similarly implanted The bowel is securely closed The abdomen may then be closed without drainage. The use of this method has greatly shortened the hospital stay of these patients and has lessened the complications which result from leakage at the site of the anastomosis Care in arranging the route of the ureter into the bowel also prevents angulation of the ureter on its way to the new site within the bowel lumen The "French cuff" of Delfino Gallo also lessens those late complications which result from ureteral reflux of bowel content into the renal pelvis

The altered body chemistry resulting from the use of the bowel as a receptacle for urine has been the subject of intensive study Early studies (22) revealed the fact that transplantation of the ureters into the small bowel invariably produced uremia The small bowel was shown to be capable of absorbing anything which the kidneys could excrete Selective absorption of some of the constituents of the urine from the large bowel was also seen to follow ureterosigmoidostomy Because of the altered chemical composition of the blood this syndrome became known as "reabsorptive hyperchloremic acidosis" (23). Women seem to be troubled less by this complication than are men Children are best able to adjust to the altered physiology engendered by uretero-intestinal transplantation

Recent experimental studies on the proper adjustment of food and fluid intake tend to show a way to prevent unfavorable reabsorption from the bowel. The irritation brought about by the outpouring of urine into the mucosa of the large bowel causes the bowel mucosa to excrete sodium into the gut lumen (24). There is a net higher reabsorption rate from the bowel lumen for chloride than for sodium The net water movement follows the osmotic gradient in direction and rate The percentage of net reabsorption of chlorides is found to be low at high total osmotic activity. The largest percentile net reabsorption of chlorides and urea occurs from the least concentrated urine specimens The greatest risk of retention of hydrogen ions is present when the amount of hydrogen ions removed from the body by the formation of a certain quantity of urine is moderate and especially if it is small in proportion to the total osmotic activity of the urine Retention of urea is more apt to occur if the urine poured into the bowel is hypotonic, and from such dilute urine a greater amount of chloride is absorbed Thus, low concentration and moderate acidity of the excreted urine promote reabsorption which produces hyperchloremic acidosis and elevation

(13 to 16) which are substituted for ureters lost through damage or disease. By this method internal drainage into the bladder is provided for the kidney, thus avoiding the many disadvantages of external fistulous drainage through an opening upon the skin.

The production of urinary receptacles for transplanted ureters has presented an ever-recurring challenge to the resourceful urologist. Transplantation of the ureters is required in removal of the bladder for vesical carcinoma and for injuries to the bladder resulting from postirradiation damage which shrinks the bladder, producing a very painful cystitis. Such changes occur in the course of treatment of recurrent cancer of the cervix. It is also occasionally necessary to remove the ureters from the bladder because of congenital deformities of the lower urinary tract. Among the current solutions for the problem of what to do with ureters removed from their normal position is a recently devised operation by which a urinary cloaca is produced from a short distal segment of a loop colostomy (17). This method has proven to be very useful, especially for those patients in whom severe postoperative irradiation cellulitis has followed secondary infection and sloughing of the intestinal mucosa and in whom vesicovaginal fistulas and vesicorectal fistulas have formed. This condition necessitates the diversion of the urinary and fecal streams followed by complete pelvic exenteration. To receive the ureters in such a patient a short, distal segment of a loop colostomy closed at its distal end is used. Such a tube of bowel is not traversed by feces. The ureters entering it are not subjected to the back pressure of fluids and intestinal gases as they are when transplanted into the closed bowel, and the proximal end of the loop which opens on to the abdominal wall comes to lie close beside the distal end of the colostomy opening which drains the large bowel. The double colostomy opening is readily covered by a Rutzen bag. This arrangement does not have the disadvantages produced by mingling urine and fecal output. Consequently, constant fecal soiling which produces the foul odor so often associated with a "wet colostomy" is avoided.

Progress in bowel sterilization (18) has continued. With present technics the large bowel which has been properly prepared may now be opened without fear of peritonitis. Accordingly in the most recently devised method of ureteral transplantation into the sigmoid (19), the bowel is opened along the anterior taenia and, through this wide-open aperture made in the wall of the sigmoid, the inside of the bowel is as clearly visualized as is the inside of the bladder in a cystotomy (20). The mucosa on the posterior surface of the sigmoid is then lifted from the muscularis at a site chosen for the transplant by means of a wheal produced by injecting 1:10,000 epinephrine in saline through a needle which pierces the mucosa (21). The elevated mucosa is incised at this point and a hemostat is passed beneath its surface. With this instrument a tunnel is created by burrowing the hemostat between mucosa and muscularis for a distance of 1.5 cm. The hemostat is then turned laterally, piercing the muscularis of the sigmoid behind the peritoneal attachment. The hemostat is opened. It seizes the distal cut off end of the ureter

the roof of the future urethra is present, a roof which lies along the ventral surface of the penis. In the succeeding days this epithelial tissue will proliferate rapidly over the raw surfaces which roof it and will form in the recesses beneath the outer skin a completely intact circular tube or urethra. This urethra, however, stops at the base of the penis. The new urethra will never extend onto the glans penis. The operation is easy to perform and accomplishes in one step results which are often not obtained by previous methods in many operative sessions It has caught the attention of surgeons everywhere.

The principle upon which this hypospadias operation is based, the ready proliferation of the urethral epithelium, became the basis for an operation devised for the surgical cure of urethral strictures (27) In this new open operation for urethral strictures known as "the buried strip technique" the urethra is opened throughout its length, exposing the entire urethra from a point well central to the most proximal of the urethral strictures all the way to the external urinary meatus The penile skin of the undersurface of the penis is now united to the cut edge of the urethral mucosa down each side of the shaft of the penis along the full length of the newly opened penis. The urethra now lies widely open When healing is complete along its entire length and all edema has disappeared, a wide strip of the urethral mucosa which previously formed the urethral roof and now is open and exposed on the under surface of the penis is outlined by incisions running along its full length just as was done in the hypospadias operation described above The edges of the skin which approximate this urethral roof on each side are undercut. Their raw approximating surfaces are apposed and pinned together with steel wire held in place by double stops, a bead and a crimped-on aluminum tube, over the urethral strip along the full length of the penis The skin edges are then carefully and minutely approximated By proliferation the mucosa which forms the roof of the urethra grows over the raw surfaces which now cover it, thus forming a new unstrictured urethra of wide caliber along the full length of the penis. This urethra, however, stops at the glans penis which, as in the operation for hypospadias, it does not penetrate. This procedure is done to remove the necessity of a life-long series of urethral dilatations. It thus warrants the short period of hospitalization and confinement made necessary in each of its two steps

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of the blood urea. To the urologist, used to urging the forcing of fluids to promote better excretion, this seems paradoxical, but it has been shown that for patients whose ureters expel their urine into the sigmoid, better levels of excretion can be obtained by following a regimen which will keep the urine both concentrated and alkaline in reaction. Reabsorption hyperchloremic acidosis may be avoided by observing this simple rule.

It is regrettable that, because of the brevity of this review, there is not opportunity for full descriptions of new surgical approaches to the kidney. Intratracheal intubation in anesthesia now permits transthoracic nephrectomies In some cases in which large renal tumors are to be removed and in which extensive lymph node dissection may be needed the transthoracic route is desirable. The transabdominal transperitoneal approach and the transabdominal retroperitoneal approach each permit the exposure of the pedicle without moving the kidney from its bed, which is a desirable feature in nephrectomy for renal malignancies Finally, there is the Nagamatsu (25) dorsolumbar approach which mobilizes the lower costal cage. In this method small segments of rib are removed from the twelfth, eleventh, and tenth ribs near their attachment to the spine. Thus freed from their posterior attachment these ribs may be elevated like a Venetian blind giving an excellent approach to the kidney or to the adrenal. This approach is especially needed when an extrapleural retroperitoneal exposure to the kidney is desired as is the case where the renal pedicle is short, the kidney is high, or a huge calculous pyonephrosis is to be removed.

Hypospadias.—A plastic operation for the repair of hypospadias has been presented which can be accomplished simply and in one step (26). It is based upon the tendency of the mucosa-like epithelium of the underside of the penis to grow prolifically in covering a defect. An incision extending from the abnormal urethral hypospadias opening distally to the edge of the glans penis is made skin-deep on each side of the strip of urethra on the under side of the penis. This strip, lying along the shaft of the penis, is left flat and intact, untouched On each side of it the skin edges are deeply undercut and lifted upward The undermining and lifting extends also to the skin over the abnormal hypospadias opening at the base of the penis To ease tension in closing these flaps across the ventral surface of the penis a longitudinal easement incision, completely through the skin, is made along the full length of the dorsum of the penis. The denuded raw surfaces of the skin flaps now approximated on the ventral surface of the penis are brought, raw surface to raw surface, over the still attached strip of penile skin, now completely hidden beneath their apposing surfaces. These apposing surfaces are pinned together with a series of steel wire sutures which pass through them from side to side and are held lightly in apposition by the pressure of a bead against the skin on each side The bead in turn is kept from slipping by a section of a small aluminum tube which is crimped onto the suture just beyond each bead. The skin edges are then very carefully sutured into fine apposition with a row of minute stitches Thus, at the end of the operation, only

ANNOTATED LIST OF REVIEWS IN MEDICINE[1]

By Eaton M. MacKay[2] and Lois L. MacKay

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Infectious Diseases

1. "Poliomyelitis," Melnick, J. L., *Advances in Virus Research*, 1, 229–75 (1953), 193 references Reviews selected aspects of current clinical and laboratory research in this field

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ADDENDUM

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47. "Quelques propos chirugicaux en marge des rapports sur la diarrhée," Cahen, J , *Acta Gastro-Enterol. (belg.)*, 17, 489–514 (1954), 94 references. The subject is well-covered.

DISEASES OF THE CARDIOVASCULAR SYSTEM

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2. "The Metabolism of the Human Heart in Vivo," Bing, R. J., *J. Mt. Sinai Hosp. N. Y.*, 20, 100–17 (1953), 45 references An excellent summary of this investigator's well-known work.

3. "Effect of Circulatory States on Determinations of Blood Volume," Gregersen, M. I., *Am. J. Med.*, 15, 785–89 (1953), 27 references. A summary for the clinical investigator.

4 "Circulatory Adjustments to Pregnancy," Burwell, C. S , *Bull Johns Hopkins Hosp* , 95, 115–29 (1954), 25 references. A broad lecture survey.

5. "Heart Disease in Pregnancy," Bergman, P., and Sjösted, T , *Acta Obstet. Gynecol. Scand* , 33, 117–61 (1954), 123 references The data in the literature along with extensive Swedish experience is carefully analyzed.

6. "The Management of Heart Disease in Pregnant Women," Burwell, C. S , *Bull. Johns Hopkins Hosp* , 95, 130–43 (1954), 15 references A conservative review of the subject

7. "Cardiac Emergencies," Gilbert, R P , *Med. Clin. N. Amer.*, 7–28 (1954), 27 references. A complete useable summary of the clinical aspects.

8. "Ubersicht der neuren kardiologischen Literatur," Grabner, G., *Wien. Z. inn. Med* , 35, 325–57 (1954), 607 references. A short survey of the cardiology literature for the first three months of the year.

36. "Arterial Angiography in the Diagnosis, Prognosis and Treatment of Occlusive Vascular Disease," Drahl, E., Pratt, G. H., and Rousselot, L. M., *Bull. N. Y. Acad. Med.*, 30, 122–31 (1954), 18 references A review designed to stress the segmental characteristic of the peripheral arterial diseases and the usefulness of angiography in their evaluation.

37. "Aneurysms: General Considerations," deTakats, G., and Pirani, C. L., *Angiology*, 5, 173–208 (1954), 66 references. A review of the general problem of aneurysms.

38 "Some Vascular Effects of Surgical Sympathectomy," Duff, R. S., *Am. J. Physical Med.*, 33, 109–17 (1954), 55 references. A most readable survey of the literature

39. "Lumbar Sympathectomy in the Treatment of Peripheral Vascular Disease," Palumbo, L. T., Quirin, L. F., and Conkling, R. W., *Postgrad Med.*, 15, 142–49 (1954), no references

40 "Peripheral Vascular Diseases," Menende, C V., and Linton, R. R., *New Engl J. Med.*, 251, 382–93, 432–38 (1954), 331 references. Advances in the field since 1949, are surveyed

41 "Sympathetic Vasodilator Outflow," Uvnäs, B., *Physiol. Revs*, 34, 608–18 (1954), 45 references. An excellent summary.

42. "Basic Mechanisms of Hemostasis," Stefanini, M., *Bull. N. Y Acad. Med*, 30, 239–77 (1954), 71 references An excellent effort to harmonize the contributions of the past decade.

43. "Thromboembolic Accidents," Julian, O C., and Dye, W. S., *Med. Clin. N. Amer*, 29–46 (1954), no references

44 "Venous Thrombosis and Thromboembolism," Madden, J L., *Am J. Surg*, 87, 909–16 (1954), 22 references. A brief review of the surgical aspects

45. "A Critical Evaluation of the Problem of Thromboembolism," DeBakey, M. E., *Intern Abstr Surg*, 98, 1–27 (1954), 447 references A complete survey of all aspects of the subject.

46. "Renal Function in Congestive Heart Failure," Youmans, W. B., *Ann. Internal Med*, 41, 739–46 (1954), 21 references. A very short review of the subject

47. "Primary Thrombosis of the Internal Carotid Artery," Ochs, L., Sensenbach, W., and Madison, L., *Am J Med*, 17, 374–82 (1954), 37 references. A review based on seven new cases.

48. "Bacterial Endocarditis," Newman, W., Torres, J M., and Guck, J. K., *Am. J. Med*, 16, 535–42 (1954), 27 references An analysis of 52 cases

49. "Embolic Mycotic Aneurysms, A Complication of Bacterial Endocarditis," Shnider, B. I., and Cotsonas, N J., *Am J Med*, 16, 246–55 (1954), 39 references A tabulation and analysis of the cases reported since 1923

50. "Current Concepts and Surgical Techniques in Cardiovascular Surgery," Nabatoff, R. A., Intern. Abstr. Surg, 97, 521–36 (1953), 99 references The literature from January, 1951, to October, 1952, is surveyed.

O. H., Dahl, J., Fry, D., and Bakken, E. E., *Am. Heart J.*, 47, 122–53 (1954), 40 references.

22. "Spatial Vectorcardiography," Grishman, A, *Advances Internal Med.*, 6, 91–131 (1954), 97 references.

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24. "Management of Hypertensive Disease," Corcoran, A. C., Dustan, H. P., Taylor, R. D., and Page, I. H., *Am. J. Med.*, 17, 383–94 (1954), 16 references. An excellent critical discussion.

25. "Pathogenesis of Essential Hypertension," Wakerlin, G. E., *Arch. Internal Med.*, 92, 889–96 (1953), 22 references. A working hypothesis is outlined.

26. "The Present Status of Surgery for Portal Hypertension," Rousselot, L. M., *Am. J. Med.*, 16, 874–77 (1954), 24 references. Primarily concerned with the problem of upper intestinal hemorrhage in this disease

27. "Hypertension in Pregnancy," Tenney, B., *New Engl. J. Med*, 249, 1108–15 (1953), 4 references. A short summary.

28. "Treatment of Hypertension," Hoobler, S W., *Am. J. Med*, 17, 259–70 (1954), 35 references. A lucid consideration of present methods.

29. "Lipoproteins, Coronary Heart Disease, and Atherosclerosis," Gofman, J. W., Glazier, F., Tamplin, A, Strisower, B., and DeLalla, O, *Physiol. Revs.*, 34, 589–607 (1954), 33 references. A detailed consideration of the role of diastolic hypertension and serum lipoproteins in the development of coronary disease.

30. "Atherosclerosis; A Problem in Newer Public Health," Keys, A., *J. Mt. Sinai Hosp. N. Y.*, 20, 118–39 (1954), 44 references An interesting discussion of this problem from an unusual point of view.

31. "Surgical Treatment of Hypertension," Morrissey, D M, *Medicine Illustrated*, 8, 161–68 (1954), 43 references. A short summary which attempts to justify surgical therapy.

32. "Pathogenesis of Arteriosclerosis," Moschcowitz, E., *J. Mt. Sinai Hosp N. Y.*, 21, 49–61 (1954), 60 references A very interesting concept is summarized

33. "Peripheral Circulation," Barcroft, H, *Ann. Rev. Physiol.*, 16, 215–42 (1954), 341 references.

34. "The Effect of the Emotions on the Peripheral Circulation," Burch, G. E., and Ray, E T, *Am J. Med. Sci*, 227, 94–101 (1954), 76 references. A timely review which should be of interest to physicians who treat patients rather than diseases

35. "Management of Arterial Hypertension," Schroeder, H. A, *Am J. Med*, 17, 540–61 (1954), 34 references Control particularly by drugs is reviewed in some detail.

Payne, F. L, *Am J. Med. Sci*, 226, 674–87 (1953), 56 references. A review of the modern approach to this problem.

DISEASES OF THE RETICULOENDOTHELIAL SYSTEM AND HEMATOLOGY

1. "Blood Volume in Health and Disease," Berson, S. A., *Bull N. Y. Acad Med.*, 30, 750–76 (1954), 128 references. A short clinical summary.

2. "The White Blood Cells in Health and Disease," Doan, C. A, *Bull N. Y. Acad. Med*, 30, 415–28 (1954), 59 references An interesting summary of the newer knowledge

3 "Present Concepts of the Structure of the Mammalian Red Cell," Ponder, E, *Blood*, 9, 227–35 (1954), 38 references A review of the subject.

4. "The Stimulus for Erythropoiesis," Root, W. S, *J Mt. Sinai Hosp N Y.*, 20, 331–38 (1954), 39 references A concise summary.

5 "Current Problems in Blood Transfusion," Vogel, P, *Bull. N Y Acad Med*, 30, 657–74 (1954), 84 references Shortcomings of the procedure are highlighted.

6 "Liste de Publications Récentes pouvant être consultées à la Bibliothèque du Centre de Transfusion Sanguine," 9, 139–47, 254–62, 424–41 (1954). A bibliography (672 references) of recent publications bearing on the problems of blood transfusion.

7. "Newer Knowledge of Human Blood Factors," Rosenfield, R. E., and Vogel, P., *J. Mt. Sinai Hosp N Y*, 20, 89–99 (1953), 63 references Newer concepts of the blood group systems are briefly outlined.

8 "A Decade of Progress in the Rh Blood-Group System," Jones, A R, Diamond, L. K., and Allen F. H, Jr, *New Engl. J Med*, 250, 283–88, 324–30 (1954), 41 references A fine review of the detailed information regarding the genetics and immunology which has accumulated during the past decade relative to this subject

9. "Clinical Implications of Plasma Fractionation," Scheinberg, I. H, *Bull N. Y., Acad Med*, 30, 735–49 (1954), 68 references The relation of [illegible]

[illegible] l of Bile Pigment," London, I. M, *B* [illegible] 4), 51 references A somewhat technical review of special interest

11. "Physiology and Pathology of Blood Coagulation," Koller, F., *Acta Haematol*, 12, 40–79 (1954), 315 references A review using abstracted [illegible]

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13 "Polycythemia Vera—Its Course and Treatment. Relation to Myeloid Metaplasia and Leukemia," Wasserman, L R., *Bull N Y Acad Med.*, 30, 343–75 (1954), 53 references A thorough analysis of our present knowledge of this disease

14 "Hemophilia," Brinkhous, K. M, *Bull N Y Acad Med*, 30, 325–

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2. "The Control of the Excretion of Water," Lewis, A. A. G., *Ann. Roy. Coll. Surg. England (London)*, 13, 36–54 (1953), 49 references A brief clinical summary.

3. "The Role of the Kidneys in the Regulation of Acid-Base Metabolism," Gilman, A., and Brazeau, P., *Am. J. Med.*, 15, 765–70 (1953), 8 references. A brief simple outline of current knowledge.

4. "Sodium Secretion by the Mammalian Kidney," Selkurt, E. E., *Physiol. Revs.*, 34, 287–333 (1954), 409 references. A complete review of the subject. Physiology.

5. "The Modern Conception of Bright's Disease," Enticknap, J. B, *Medicine Illustrated*, 8, 349–56 (1954), 35 references. A point of view largely determined by the British literature.

6. "Renal Tubular Failure of Shock and Nephritis," Van Slyke, D. D., *Ann. Internal Med.*, 41, 709–38 (1954), 64 references. The topic is covered in a beautiful manner which is easily read and authoritative.

7. "Dialysis in Treatment of Uremia," Kolff, W. J., *Arch. Internal Med*, 94, 142–60 (1954), 77 references. A critical evaluation of the artificial kidney and peritoneal lavage.

8. "The Role of the Artificial Kidney in the Treatment of Uremia," Morales, P. A., Gordon, S. G., Pinck, B. D., and Hotchkiss, R. S, *Surg Clin. North Amer.*, 423–40 (1954), 27 references. Recent literature and the author's experience is reviewed.

9. "Les Problemes de la Transplantation Renale," Antoine, B, and Ducrot, H., *J. d'Urologie*, 60, 289–329 (1954), 234 references. A review of all aspects of the subject.

10. "Hydronephrosis," Prather, G. C., *New Engl. J. Med.*, 250, 944–52 (1954), 43 references. A review of the anatomic, physiologic, diagnostic, and surgical aspects of the subject.

11. "Diagnosis and Surgical Management of Obstructive Uropathy in Chil[illegible] 88 239–[illegible]

1[illegible] *Clin. N. Amer.*, 1461–74 (1954), 25 references Causes and remedial measures are well-discussed.

13. "Nephrocalcinosis· A Review," Mortensen, J. D., and Baggenstoss, A. H, *Am J. Clin. Pathol.*, 24, 45–63 (1954), 84 references. A clinical review.

14. "Ureterocele, its Etiology, Pathogenesis and Diagnosis," Wershub, L. P., and Kirwin, T. J., *Am. J. Surg.*, 88, 317–27 (1954), 44 references. A careful review of the literature.

15. "Stress Urinary Incontinence in the Female," Mikuta, J. J., and

28. "Hyaluronidase der Samenzellen und Sterilität," Ploberger, U., *Z. Vitamin-Hormon-u. Fermentforsch*, 6, 64–71 (1954), 59 references The literature of recent years is summarized.

29. "Physiological Significance of Lymph Drainage of the Serous Cavities and Lungs," Courtice, F. C., and Simmonds, W. J., *Physiol. Revs*, 34, 419–48 (1954), 166 references. A review of our understanding of lymphatic absorption from serous cavities and the functional significance of the pulmonary lymphatics

30 "Die Glykolypse- und Atmungsfermente der Leukozyten," Bruckel, K W., and Remmele, W., *Z. Vitamin-Hormon-u Fermentforsch.*, 6, 50–63 (1954), 82 references. A review of the literature.

31. "Die Fibrinolyse in der Klinik," Schmid, J, *Wien. Z. inn. Med*, 35, 83–96 (1954), 152 references A concise summary of the literature

NUTRITION AND NUTRITIONAL DISEASES

1. "Energy Metabolism," DuBois, E F, *Ann. Rev Physiol*, 16, 125–34 (1954), 96 references

2 "Nutrition," Phillips, P. H., and Constant, M A, *Ann. Rev. Biochem*, 23, 319–44 (1954), 198 references

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4. "Vitamin C Requirement of Human Adults," Bartley, W., Krebs, H. A, and O'Brien, J. R. P., *Med Research Council Brit*, Spec Rept. Ser. No 280, 1–179 (1953), 99 references An extensive study

5. "Fat-Soluble Vitamins," Quaife, M. L, *Ann Rev. Biochem*, 23, 215–44 (1954), 299 references.

6. "Water-Soluble Vitamins," Smith, E. L, Cheldelin, V. H., and Kind, T. E, *Ann Rev Biochem*, 23, 245–318 (1954), 531 references

7. "Diagnosis of Malnutrition in Man," Thomson, A M, and Duncan, D L, *Nutrition Abstr & Revs*, 24, 1–18 (1954), 111 references A critical review of a complex area

8. "Annual Review of Literature on Fats, Oils and Soaps, Physiology and Biochemistry," Piskur, M. M, *J Am Oil Chemists' Soc*, 30, 228–32 (1953), 186 references A brief but complete summary

9. "Body Fat in Adult Man," Keys, A, and Brozek, J, *Physiol Rev*, 33, 245–325 (1953), 298 references. A complete review of the literature and the subject Most useful for reference purposes

10. "Genetic, Traumatic and Environmental Factors in the Etiology of Obesity," Mayer, J., *Physiol. Revs*, 33, 472–508 (1953), 256 references A broad discussion of the factors producing obesity

11. "Obesity," Walker, H. C., *Arch Internal Med*, 93, 951–66 (1954), 78 references. A review of the complications and sequelae

12. "Nutritional Factors and Liver Diseases," Swarz, K, *et al*, *Ann.*

41 (1954), 30 references. A concise, somewhat general, but complete consideration of the subject.

15. "*Hemophilia and Hemophilia-like Diseases Caused by Deficiencies* in Plasma Thromboplastin Factors," Rosenthal, R. I., *Am. J. Med*, 17, 57–69 (1954), 31 references. The place of the factors—anti-hemophilic globulin, plasma thromboplastin component, and thromboplastin antecedent—is well-reviewed.

16. "Symposium on Hemophilia," Dameshek, W., *et al.* (11 other authors), *Blood*, 9, 244–93 (1954), 163 references A collection of ten papers presenting very different points of view.

17. "Reticuloendotheliosis," Klemperer, P., *Bull N. Y. Acad. Med*, 30, 526–37 (1954), 10 references A review of a group of heterogeneous maladies with a fairly successful effort to integrate them.

18 "The Lymphomas and Leukemias," Rosenthal, N., *Bull N. Y. Acad. Med.*, 30, 583–600 (1954), 34 references A brief discussion of the various aspects of these diseases based in part on an analysis of some 600 patients.

19. "The Treatment of Leukemia," Burchenal, J. H., *Bull. N. Y. Acad Med.*, 30, 429–47 (1954), 38 references A review of the practical aspects of the problem

20. "The Hereditary Anemias," Watson, R J, *Bull. N. Y. Acad. Med*, 30, 106–21 (1954), 27 references. A first-rate summary of the subject.

21. "Vitamin B_{12} and Megaloblastic Anemia: Recent Studies," Sacks, M. S., *Ann. Internal Med*, 40, 375–80 (1954), 29 references. A very brief but complete review of recent studies.

22. "Drug-Induced Hypoplastic Anemias and Related Syndromes," Osgood, E. E., *Ann. Internal Med.*, 39, 1173–88 (1953), 59 references. A concise review of current concepts of the diagnosis and therapy of hypoplastic anemias and the closely related conditions, erythrocytic, granulocytic, and thrombocytic hypoplasia

23. "Anemias in Infancy and Childhood: Diagnostic and Therapeutic Considerations," Smith, C. H., *Bull. N. Y. Acad. Med*, 30, 155–83 (1954), 33 references. A most useful outline of clinical interest with wide application in the field of adult medicine as well as pediatrics.

24. "Thrombotic Thrombocytopenic Purpura," Singer, K., *Advances Internal Med*, 6, 195–234 (1954), 127 references. An ailment which is occurring or being diagnosed with increasing frequency.

25. "The Thrombocytopenic Purpuras," Lozner, E. L., *Bull. N. Y Acad. Med.*, 30, 184–94 (1954), 31 references. The differential, pathogenesis, and treatment of these diseases is summarized in an excellent manner.

26. "The L. E. Cell Phenomenon," Hargraves, M. M., *Advances Internal Med.*, 6, 133–60 (1954), 54 references An excellent review of an all-important method for the study of systemic lupus erythematosis

27. "The Mechanism of Glucocorticoid Eosinopenia," Esselier, A F, Jeanneret, R. L., and Morandi, L, *Blood*, 9, 531–49 (1954), 58 references An analytical review.

13. "Summary of Known Metabolic Functions of Nicotinic Acid, Riboflavin and Vitamin B_6," Snell, E E., *Physiol. Revs.*, 33, 509–24 (1953), 109 references Biochemical.

14 "Metabolic Functions of Pantothenic Acid," Novelli, G. D , *Physiol. Revs*, 33, 525–43 (1953), 100 references. Biochemical.

15 "Metabolic Functions of Thiamine and Lipoic Acid," Read, L. J., *Physiol. Revs*, 33, 544–59 (1953), 64 references. Biochemical.

16 "Metabolic Functions of Biotin," Lardy, H. A., and Peanasky, R., *Physiol. Revs* 33, 560–65 (1953), 31 references. Biochemical

17 "Some Abnormalities of Vitamin B_6 Metabolism in Human Beings," Vilter, R W., Biehl, J. P., Mueller, J. F., and Briedman, B. I , *Federation Proc.*, 13, 776–79 (1954), 34 references. A very short survey of recent literature.

18. "Physiologie, Pathologie und Biochemischer Wirkungsmechanisms der B_{12}-Vitamine," Heinrich, H. C., and Lahann, H , *Z. Vitamin-Hormon-u Fermentforsch*, 6, 126–200 (1954), 222 references This is the first section, i e, Physiology, of a larger review and covers the literature intensively.

19 "Recent Studies of Intrinsic Factor and the Utilization of Radioactive Vitamin B_{12}," Schilling, R F., *Federation Proc*, 13, 769–75 (1954), 52 references. A provocative review of the literature

20 "Porphyria," Watson, C. J , *Advances in Internal Med*, 6, 235–99 (1954), 164 references An excellent review of all phases of the subject.

21. "The Gonadal Function in Male Diabetics," Bergqvist, N , *Acta Endocrinol*, 15, Suppl. 18, 1–29 (1954), 36 references The literature and excellent new data is analyzed.

22. "Hepatomegaly and Diabetes Mellitus," Goodman, J. I., *Ann Internal. Med.*, 39, 1077–87 (1953), 43 references A critical summary of a large series of patients.

23. "Emergency Complications of Diabetes Mellitus," Goldinger, J M., *Med. Clin N Amer.*, 183–97 (1954), 4 references Standard procedures are outlined

24. "Biochemical Aspects of Atherosclerosis," Gould, R G, *J Am Geriatrics Soc*, 10, 640–49 (1954), 38 references A brief summary of the recent literature.

25 "Uric Acid: Its Role in Biological Processes and the Influence upon it of Physiological, Pathological and Pharmacological Agents," Bishop, C., and Talbott, J. H , *Pharmacol. Revs.*, 5, 231–73 (1953), 372 references A thorough review of minor clinical interest.

26. "Gout," Rosenberg, E F , *J. Am Geriatrics Soc*, 2, 229–39 (1954), 9 references [illegible]

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28 "History of the Use of Colchicum and Related Medicines in Gout," Hartung, E. F., *Ann. Rheumatic Diseases*, 13, 190–200 (1954), 126 references

N. Y. Acad. Sci., 57, 615–961 (1954), 715 references. A symposium composed of 36 papers by 63 authors.

13. "Nutritional Effects of Antibiotics," Jukes, T. H., and Williams, W. L., *Pharmacol. Revs.*, 5, 381–420 (1953), 220 references A summary of current knowledge primarily in the field of fowl and animal feeding but including the sparse data available for man.

14. "Antibiotics in Animal Nutrition," Stokstad, E. L. R., *Physiol. Revs*, 34, 25–51 (1954), 232 references. Of interest here because of the possible transfer of information to human nutrition.

15. "Role of Wheat and Wheat Products in Human Nutrition," Hegsted, D. M, Trulson, M. F., and Stare, F. J., *Physiol. Revs*, 34, 221–58 (1954), 193 references A consideration of the more important literature.

DISEASES OF METABOLISM

1. "Considerations Concerning the Pathways of Synthesis in Living Matter," Krebs, H. A., *Bull. Johns Hopkins Hosp.*, 95, 19–33 (1954), 31 references. A very general survey.

2. "Intermediary Metabolism," Villee, C. A., *New Engl. J. Med.*, 251, 21–28, 64–70 (1954), 124 references. A good review of some of the recent changes in concepts of the pathways of intermediary metabolism

3. "Biological Oxidations," Anfinsen, C. B, and Kielley, W. W., *Ann Rev. Biochem.*, 23, 17–54 (1954), 205 references

4. "Water and Electrolyte Metabolism," Mannery, F. J., *Physiol. Revs.*, 34, 334–417 (1954), 629 references. A very complete summary of chemical morphology of the mammal.

5 "Mineral Metabolism (Animal)," Davis, G K., *Ann. Rev Biochem*, 23, 459–80 (1954), 248 references.

6 "Iron Metabolism," Granick, S., *Bull. N. Y. Acad. Med.*, 30, 81–105 (1954), 51 references. Generally a nonclinical review of the functions of various iron compounds in the organism and the general metabolism of iron.

7. "Proteolytic Enzymes," Desnuelle, P, *Ann. Rev. Biochem*, 23, 55–78 (1954), 152 references.

8. "Nonoxidative and Nonproteolytic Enzymes," Kalckar, H. M, and Klenow, H., *Ann Rev. Biochem*, 23, 527–86 (1954), 334 references.

9. "Carbohydrate Metabolism," Weinhouse, S, *Ann. Rev. Biochem*, 23, 125–76 (1954), 264 references

10. "Current Concepts of the Action of Insulin," Stadie, W. C, *Physiol. Revs*, 34, 52–100 (1954), 107 references. A summarizing of the more recent developments for the physiologist and metabolic expert.

11. "Clinical Effects of Analogs of Folic Acid, Purines, Pyrimidines, and Amino Acids," Burchenal, J H, *Federation Proc.*, 13, 760–68 (1954), 99 references. An interesting venture into a field of great potential importance.

12. "Metabolic Studies on Histidine, Histamine, and Related Imidazoles," Tabor, H., *Pharmacol. Revs*, 6, 299–343 (1954), 413 references The literature is completely covered.

389–430 (1953), 111 references. A summary of its developmental course comparative anatomy, and possible physiologic functions.

16 "Electrolyte Disturbances in Adrenal Diseases," Knowlton, A. I., *Am J. Med.*, 15, 771–76 (1953), 32 references. A clear, short summary of the current situation

17. "The Parathyroids," Bartter, F. C., *Ann Rev Physiol.*, 16, 429–44 (1954), 117 references.

18. "Thyroid Hormones and Iodine Metabolism," Roche, J., and Michel, R., *Ann. Rev Biochem*, 23, 481–500 (1954), 205 references

19. "Progressive Exophthalmos," Naffziger, H. C., *Ann Roy Coll Surgeons Engl*, 15, 1–24 (1954), 38 references A first-hand review of a still incompletely understood sign

20. "Radioactive Iodine in Hyperthyroidism," Nelson, T. S., Raiman, R J., and Clark, D. E., *Med Clin. N Amer.*, 555–59 (1954), five references An optimistic summary.

Allergy

1. "Miscellaneous Review of Allergy," Halpin, L. J., *Ann Allergy*, 12, 299–350 (1954), 157 references. A review of articles selected from the literature of 1953.

2. "Pediatric Allergy," Ratner, B , *Ann Allergy*, 12, 198–228 (1954), 93 references A critical review of the 1953 literature.

3. "Treatment of Allergic Emergencies," Talmage, D W , *Med Clin. N Amer.*, 63–73 (1954), 12 references. A summary which might prove useful to any physician.

4. "Allergy in Infancy and Childhood," Burrage, W. S , Burgin, L. B , Wang, D. M. K., and Irwin, J W., *Med Clin N Amer.*, 1255–79 (1954), 25 references An outline of current methods of treatment.

5. "Hay Fever," Kaplan, M. A , Ehrlich, N J., and Aaronson, A L., *Ann. Allergy*, 12, 92–120 (1954), 219 references. A complete review of the literature for 1952.

6 "Pyromen in Allergy," Randolph, T. G , *Med Clin. N Amer.*, 561–568 (1954), 37 references. Evidence favoring the nonspecific usefulness of this fever-producing compound.

7. "Adrenocortical Hormones in Infection and Immunity," Kass, E H , and Finland, M., *Ann. Rev. Microbiol* , 7, 361–88 (1953), 313 references

8. "The Immunological Response," Haurowitz, F , *Ann Rev Microbiol.*, 7, 389–414 (1953), 252 references.

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1. "Chemical Constitution and Carcinogenic Activity," Badger, G M , *Advances in Cancer Research*, 2, 73–127 (1954), 113 references. Chemical pharmacology.

An excellent historical review with emphasis on the currently unsolved problems in its action.

29. "Butazolidin in the Treatment of Gout," Steinbocker, O., Newstadt, D. H., and Ehrlich, M., *Med. Clin. N. Amer.*, 611–24 (1954), 58 references. A critical evaluation and comparison with other therapeutic agents

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1. "Growth," Sontag, L. W., and Garn, S. M., *Ann. Rev. Physiol.*, 16, 37–50 (1954), 105 references.

2. "Variations in Human Body-Build," Lindegård, B., *Acta Psychiat et Neurol. Scand.*, Suppl. 86, 1–163 (1953), 113 references. The literature and a collection of Norwegian data is analyzed.

3. "Physiological Mechanisms in Development," Spratt, N. T, Jr, *Physiol. Revs.*, 34, 1–24 (1954), 210 references. Highly specialized.

4. "Secular Change in the Height of British Adults," Boyne, A. W., *Nutrition Abstr. & Revs.*, 24, 255–69 (1954), 34 references. A detailed study.

5. "Recent Trends in the Biochemistry of the Steroid Hormones," Lieberman, S., and Teich, S., *Pharmacol. Revs.*, 5, 285–380 (1953), 569 references A broad survey of all aspects of the subject.

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